UNIVERSITY OF MICHIGAN
JUN 25 1954
MEDICAL LIBRARY

THE AMERICAN JOURNAL of HUMAN GENETICS

VOLUME 6 — *June 1954* — NUMBER 2

The Problem of Adaptive Differences in Human Populations
Theodosius Dobzhansky and Bruce Wallace 199
Implications of Some Recent Developments in Hematological and Serological Genetics
James V. Neel 208
Blood Factor Incompatibility in the Etiology of Mental Deficiency *Emanuel Hackel* 224
A Case of Syndactylism of the Ring and Little Fingers *Alfred T. Collette* 241
Fistula Labii Inferioris Congenita and Its Association with Cleft Lip and Palate
Anne Van Der Woude 244
An Extension of Two Pedigrees of Hypoglycemosis
R. C. Anderson and Irvine McQuarrie 257
Evidence for a Hereditary Factor in Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome) *Julius D. Metrakos and F. Clarke Fraser* 260
Blue Sclerae, Fragilitas Ossium, Arachnodactyly and Deafness in an Indian Family
Phillip V. Tobias 270
The Mutation Rate of the Rh-Loci—a Critical Review *Friedrich Vogel* 279
Sex Ratio of White Births in the United States During the Second World War
Brian MacMahon and Thomas F. Pugh 284
Book Review 293
Bibliography of Human Genetics *V. Rae Phelps* 295

Published Quarterly by

THE AMERICAN SOCIETY OF HUMAN GENETICS

THE AMERICAN JOURNAL OF HUMAN GENETICS

is a quarterly record of research, review and bibliographic material relating to heredity in man, and to the applications of genetic principles in medicine, anthropology, psychology, and the social sciences. It is owned and controlled by the American Society of Human Genetics, and is edited by a staff appointed by its Board of Directors.

Editor:
HERLUF H. STRANDSKOV
University of Chicago

Associate Editors:

C. NASH HERNDON
Bowman Gray School of Medicine

HORACE W. NORTON
University of Illinois

NORMA FORD WALKER
University of Toronto

MADGE T. MACKLIN
Ohio State University

BRONSON PRICE
U.S. Children's Bureau, Washington

ALEXANDER S. WIENER
Chief Medical Examiner's Office, New York City

Subscription, per volume, $8.00 *Single numbers,* $2.50

THE American Journal of Human Genetics is published quarterly at Baltimore, Md. in March, June, September, and December. A volume will consist of four numbers, totaling approximately 400 pages. Subscription and other business communications should be addressed to the publishers, The American Society of Human Genetics, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, or to the Treasurer, Dr. C. Nash Herndon, Department of Medical Genetics, Bowman Gray School of Medicine, Winston-Salem, North Carolina, U.S.A. Remittance for subscriptions from countries other than the United States must be payable in U. S. currency or its full equivalent. Checks or money orders should be made payable to the American Society of Human Genetics.

Copyright, 1954, by the American Society of Human Genetics. All rights reserved
Made in United States of America

The American Journal of Human Genetics

Vol. 6 No. 2 *June 1954*

The Problem of Adaptive Differences in Human Populations[1]

THEODOSIUS DOBZHANSKY AND BRUCE WALLACE

Institute for the Study of Human Variation, Columbia University, New York, and Long Island Biological Laboratory, Cold Spring Harbor

THE SALIENT CHARACTERISTIC of the first half-century of the development of genetics was a concentration of the attention of geneticists on studies of genes which produced discrete, discontinuous, and easily classifiable phenotypes. Bateson, who was more than any other single person responsible for the direction of the fledgling science, emphasized that heredity is transmitted in lumps and that evolution occurs in jumps. Morgan and his co-workers experimented chiefly with "good" mutants, which differed so clearly from "normal," or "wild-type," flies that even beginning students could be expected to make not too many mistakes in classification. Human genetics amounted chiefly to enumeration of diseases and malformations which were dominant or recessive to the "normal" condition. "Bad" mutants involving slight changes in the Drosophila phenotype were known to occur, but most of them were disposed of by washing them down the drain. In man, many traits were known to "run in families," but little was done to study them, unless they could be squeezed into the classical framework of the 3:1 ratio.

The preoccupation with discrete gene effects was, no doubt, reasonable and expedient. One learns arithmetic before trigonometry, and simple tunes before symphonies. "Bad" mutants are useless when one experiments with linkages and tries to build chromosome maps. When simple Mendelian inheritance still seems puzzling and recondite to many people, it is futile to expound to them the mysteries of population genetics. But, in science, the time usually comes when oversimplification becomes misleading and directs the thinking into wrong channels. It looks as though human genetics is on the verge of this situation.

The purpose of the present article is to submit the possibility that genes with phenotypically discrete effects may represent, in the main, a rather special class of genetic variants, particularly from the standpoint of their adaptive significance in populations. A comparison of human populations with the ge-

Received March 8, 1954.

[1] Paper read at the Symposium on Genetics and the Races of Man, sponsored by the American Society of Human Genetics, the Genetics Society of America, the Society for the Study of Evolution, and the A.A.A.S., Section H-Anthropology, on December 30, 1953.

netically better known populations of certain species of Drosophila is enlightening in this connection.

A sample of a natural population of most species of Drosophila can usually be described as consisting of "normal" or "wild-type" flies. To be sure, some individuals are found which are larger or smaller, somewhat lighter or darker, than the average. However, these variations are mostly environmental in origin, and depend chiefly upon temperature and food supply with which these flies had grown and developed. Very sporadically, a strikingly aberrant individual is found among masses of "normals." Some of these aberrations are identical with the laboratory mutants depicted in textbooks of genetics. Chetverikov in 1927, and many investigators since then, demonstrated that the uniformity of "normal" individuals is, in part, spurious. Many, in fact a majority, of the individuals which occur in nature are heterozygous for recessive genes or gene complexes which produce various abnormalities in homozygous condition. Not a few of these hidden or concealed recessives are lethal when homozygous. Others are semilethal or subvital, i.e., produce what may be described as more or less grave hereditary diseases. Still others cause sterility of homozygous females or of males, or, rarely, of both sexes. Many of the homozygotes grow and mature more slowly, and an occasional one develops more rapidly, than do the normal controls. Finally, some of the homozygotes show various malformations of visible morphological traits. It is this last class of genetic variant that has yielded the most valuable materials for the classical genetic studies.

The genetic structure of natural populations of Drosophila is, then, quite parallel to that of human populations. In either case, we observe a scattering of genetically aberrant individuals, among masses of "normals," the aberrations being frankly pathological in their effects. Far more numerous than the phenotypically expressed hereditary diseases and malformations are the concealed recessive ones which are carried in apparently normal individuals, and which appear on the phenotypic surface chiefly as a result of inbreeding.

The frequency of defective germ plasm carried in Drosophila populations is amazingly high. If an eugenical movement existed among Drosophilae, some of its adherents would probably fear that the flykind is about to go into a genetic tailspin. There is no way at present to decide whether the gene pool of human populations is riddled with deleterious mutants to an extent greater or lesser than that of Drosophila. One thing is certain however: deleterious recessives are bound to accumulate up to a certain point in populations of any sexually reproducing species the genes of which are subject to mutation. The degree of the accumulation will depend on the rates of mutation and on several other variables which can not be discussed here. Suffice it to say that the production of deleterious mutants is the price which a living species pays for retaining the evolutionary advantages of genetic plasticity. This is as true of man as it

is of Drosophila. Here a geneticist can afford to be dogmatic: Studies on fly populations bring to light certain fundamental biological regularities to which all sexual species, including the human species, are subject.

It is, however, a different aspect of the situation which interests us here. A great majority of the discrete mutants found in the gene pool of natural populations, whether of man or of Drosophila, are deleterious. It is true that some of them may be neutral or even useful in some environments, but most of them seem to be unconditionally harmful. It is, indeed, hard to imagine environments in which homozygous amaurotic idiocy or epiloia could possibly be useful. These mutants are genetic debris generated as by-products of adaptive evolution.

A harmful dominant or a semidominant may persist in a population for many generations before it is finally expunged from the gene pool. Hence, some individuals are afflicted with achondroplasia, Huntington's chorea, hemolytic jaundice, glaucoma, and dozens of other diseases and malformations which yield pedigrees that look so beautiful on paper. It is further known that deleterious recessives persist in populations for many generations after their origin. Here belong such classic examples of recessive inheritance in man as albinism, amaurotic idiocy, xeroderma pigmentosum, thalassemia, sicklemia, and other adornments of genetics textbooks and of programs of genetics meetings.

Contrast with the above frankly deleterious variants, the genes responsible for intra-populational polymorphism and for inter-populational differences. Here belong the blood antigens, the biological function of which still remains to be clarified. Further, there is the inchoate mass of genetically complex, polygenic, quantitatively variable, and often environmentally easily modifiable traits. Human populations vary with respect to such obvious characters as skin, hair, and eye colors; hair shape; height, weight, proportions of various body parts, constitution, many metabolic traits, resistance to infections and degenerative diseases, and finally many psychic traits.

The reason why these obvious human characters are genetically little known is that they are notoriously refractory to study. You do not get with them either clean-looking pedigrees or gene schemes that can be safely shown to critically-minded colleagues or to an elementary genetics class. These characters are polygenic. The time has come when they can no longer be ignored, and certain findings made in Drosophila populations may throw light on their biological roles and on possible approaches to their investigation.

As stated above, many chromosomes in natural populations of Drosophila produce when homozygous all kinds of physiological and morphological abnormalities and malformations. For some years this situation has been interpreted as due only to a time lag in the elimination of deleterious recessive mutants by natural selection. It now begins to appear that this interpretation was an oversimplification. Wallace and Madden (1953) have developed some

refined analytical techniques. Using these, Dobzhansky and Spassky (1953), found that almost every chromosome in natural populations of certain species of Drosophila is more or less deleterious when homozygous. Wallace and Madden themselves observed a similar situation develop within only some tens of generations in their irradiated and control experimental populations of *Drosophila melanogaster*.

"Normal" individuals, of which natural populations are mostly composed and on which rests the genetic welfare of the species, have, then, a rather startling genetic structure. Most of these individuals carry the two chromosomes of each pair capable of producing more or less severe impairments of fitness if they were allowed to become homozygous. The "normal" fitness of a species is, then, simply an average product of a multitude of genotypes all riddled with deleterious recessives. What is the origin of this puzzling situation? It may well be that the mutation pressure is so relentless that almost every individual becomes a carrier of several harmful mutant genes. This is precisely the picture of the genetic status of human populations arrived at by Muller (1950) in his brilliant and portentous Presidential Address to the Society of Human Genetics.

One may carry the analysis of the situation in Drosophila somewhat farther. As pointed out by Muller and others, complete recessivity is uncommon. Heterozygosis for mutant genes which are deleterious when homozygous may, then, reduce the fitness of heterozygotes below the theoretical maximum level of fitness expected in individuals free of all deleterious mutants. Flies, or men, free of deleterious heterozygosis, should have a fitness above the average actually found in nature. Such "superflies" and "supermen" have not however been obtained so far, and there are reasons to doubt that they will be easily obtainable. Indeed, some gene complexes which are deleterious when homozygous have unexpected effects when heterozygous.

Wright, Dobzhansky, and Hovanitz (1942) showed that recessive autosomal lethals found in natural populations of *Drosophila pseudoobscura* produced, on the average, a reduction of the fitness of heterozygotes. Stern et al. (1952), Wallace and King (1952), Cordeiro (1952), and Prout (1952) found this to be true also in *Drosophila melanogaster* and *Drosophila willistoni*. However, not all lethals behave in this way. Stern et al. (1952), Cordeiro (1952) and Cordeiro and Dobzhansky (1954) found that some lethals had no detectable effects on the fitness of heterozygotes, and still other lethals gave slight but quite real improvements in heterozygotes. Furthermore, Cordeiro and Dobzhansky showed that the same lethal can be deleterious in combination with some genes and heterotic with others. Whether a gene is deleterious or heterotic is often due not alone to the properties of that gene but of the gene plus the rest of the genotype of the individual in which it is found. Heterotic lethals, or recessive hereditary diseases which increase the fitness of their heterozygous carriers seem to be as yet unknown in *Homo sapiens*, but we

might be well advised to keep in mind the possibility of their being found. A gene which causes a disease or a malformation when homozygous may be favorable in heterozygotes.

When heterozygotes exceed the homozygotes in fitness, balanced polymorphism is the result. Selective forces retain in populations gene alleles and gene complexes which produce heterosis, even if these genes and complexes are deleterious or lethal when homozygous. Natural selection thus may perpetuate potential hereditary diseases. This possibility is realized in many Drosophila populations which are mixtures of individuals with differently built chromosomes, the differences between which are due to inversions of blocks of genes. Some homozygotes are less than half as fit as the heterozygotes, and yet such semilethal genotypes are produced in nature at finite rates. Now, recent work in Drosophila, and of Lerner and his colleagues in domestic animals, indicates that heterosis is an adaptive mechanism of utmost importance in populations of sexually reproducing and normally outbreeding species. Man, at least at the present time, clearly belongs to the category of such species (it might have been more inbred in the past).

In outbred species, the two chromosomes of each pair which an individual receives from its parents are, as a rule, descended from separate lines of descent for many generations. Now, an individual may be highly fit regardless of how deleterious some of his chromosomes would be if present in double dose. The important consideration here is that no gene allele and no linked gene complex which is deleterious when homozygous occur in many unrelated individuals in a population. The limiting case, probably never reached in reality, would be when no gene allele or gene complex is present in a population more than once. The situation in most populations is stabilized short of this limit, but there is a trend of natural selection increasing the diversity of gene alleles and complexes until most of them are individually so rare that the ill-adapted homozygotes will be seldom formed. Such homozygotes appear chiefly in families where marriages of relatives have taken place. The average adaptive level of the population is kept as high as the fitness of an average heterozygote will allow.

Classical genetics referred to flies which live in natural habitats as being "normal" or representing the "wild-type." Recent work has undermined these concepts, except as very rough standards which can be used to facilitate the description of mutants of the kind which are used in classrooms. In reality, individuals of which natural populations are composed are more or less complex heterozygotes, and moreover no two of them are likely to have the same genotypes. They are "normal" only in the sense that they usually lack gross malformations or hereditary diseases. Otherwise, there exist as many kinds of "normal" flies as the patience of the investigator might permit him to distinguish (Cordeiro and Dobzhansky 1954). In detail, the genetic situation

varies from species to species, and the information available at present does not suffice to form a safe basis for generalizations. There is some reason to believe that species which are widespread, common, and ecologically versatile are genetically most variable, show most pronounced heterosis, and suffer most from inbreeding. Rare and ecologically specialized forms are relatively resistant to inbreeding (Dobzhansky and Spassky, 1954).

Concerning the human species, our knowledge is pitifully inadequate. However, every person is different from every other person in many respects, and the weight of the evidence certainly suggests that the differences between persons, excepting monozygotic twins, are to varying extents genetically conditioned. The concept of wild-type has never been considered polite for men, and being "normal" has meant only freedom from gross pathology and from outstanding intellectual accomplishment. Nevertheless, the genetic differences among "normal" men can not be ignored. It is very likely that they reflect the basic structure of the gene pool of human populations, that they furnish the genetic means whereby the populations retain their hold on diversified and variable environments, and finally that genetic differences serve as a leaven of creative accomplishment. And yet, these differences are so difficult to analyze in the conventional terms of 3:1 ratios that most geneticists have preferred to leave them alone for the time being.

The work on population genetics of sexual species thus points towards distinguishing two categories of genetic variants in populations of such species, including man. First, there are the deleterious mutants, any one of which is likely to be ephemeral in a given population, although they appear again and again in different times and places, and although any one population usually contains many of these mutants. Some of the deleterious mutants are dominant, and others are recessive. The recessivity is often incomplete, making the mutant deleterious not only when homozygous but, to varying extent, also when heterozygous. Their existence is an unavoidable consequence of the occurrence of mutation and of the less than perfect efficiency of natural selection. It is this category of genetic variants which Muller chiefly considered in his Presidential Address (1950), and this category has yielded a large majority of the known clear-cut examples of Mendelian inheritance in man.

The second category comprises gene alleles and linked gene complexes which are more or less permanent constituents of the gene pool of a population. It is a curious fact that most of these genetic variants are to some extent deleterious when homozygous, and yet their manifold heterozygous combinations engender the endless diversity of the genotypes which attune the species to its environments.

Adaptive evolution on racial and specific levels is brought about by the repatterning of the gene pool by means of sexual recombination, which generates new gene complexes some of which may be better suited to changing environ-

mental conditions. The phenotypic traits determined by the genetic variants of this second category rarely display schematically clear hereditary transmission. Two reasons for this may be suggested. One is the multiplicity of alleles at many gene loci, and especially the multiplicity of alternative gene complexes in many chromosomes. The second reason is that many of the physiologically and ecologically important traits of a species are polygenic. Polygenic traits have many degrees of phenotypic expression, which makes possible a great precision of genetic adaptation of the population to its environment.

It is obvious that the two categories of genetic variants briefly characterized above are not sharply distinct. Nature seldom conforms to our simple schemes. The history of genetics has seen several attempts to assert a fundamental dualism of heredity, and to set up alternative classes of major and minor genes. None of these attempts proved successful. Nevertheless, studies on polygenic inheritance obviously require different methods than those used to apprehend the simple 3:1 or 1:1 segregations. Nobody doubts the reality of youth and old age, although the former slides into the latter imperceptibly. The genetic complexity of most "normal" human traits which vary within and between populations is too striking a fact to be ignored, especially since studies on animal populations are beginning to unravel the evolutionary basis of this complexity.

It can hardly be an accident that, apart from hereditary diseases and malformations, the human traits which show the most clearcut and unencumbered Mendelian segregations are found chiefly among blood antigens (Boyd 1950, Dobzhansky 1951). This is a consequence of the methods used for the detection of the antigenic traits. The polymorphism of blood antigens in human populations is studied by means of techniques which uncover chemical differences that are believed by many geneticists to be fairly close to the primary products of gene action. Now, polygenic determination of phenotypic traits is a result of interaction of many gene products in the process of development. It is, then, a good working hypothesis that, if it were possible to extend our analytical methods down to the developmental level of primary gene effects, or at least close to this level, then a complete definition and discreteness of all genetically variable traits would result. This hypothesis has proved successful in the analysis of some traits, as exemplified in the brilliant work of Neel, Pauling, Itano, and others on varieties of human hemoglobins. There is no question that the range of applicability of such techniques can and should be extended. A hope that they may be applicable to the analysis of all polygenic traits seems however somewhat unrealistic at present.

Human geneticists will have to become used to deal with traits which show segregations in families, but which are influenced by so many genes that the discreteness of the pheno- and genotypic classes is obliterated when studied in populations. Here belong such obvious traits as eye colors, hair colors, hair

shapes, and possibly some adaptively significant metabolic traits, as revealed by chromatographic analysis of urine and saliva (Berry 1954 and unpublished data). Genetically even more complex, and environmentally more variable seem to be such traits as stature, body build, and head shape. It is perhaps not too pessimistic to think that these traits may not be completely analyzed in terms of individual genes within the predictable future. Such an analysis is not however essential for the progress of genetic studies.

The more basic problem which a geneticist has to face is the adaptive architecture of individual genotypes and of the gene pool of the human species and its racial subdivisions. Experimental work on animal populations will be invaluable in blazing the trail for an eventual understanding of the genetic structure of the human species and of the processes which operate in human populations. In this connection, the work of our colleagues Vetukhiv (1953 and unpublished data) and Brncic (1954) is suggestive. Vetukhiv has studied local races of *Drosophila pseudoobscura* from certain parts of California, Utah, and Colorado. He compared the viabilities of the populations from several localities with those of the F_1 and F_2 hybrids between the same populations. He found that the F_1 hybrids usually show a heterosis, an increased viability comparent to the parental populations. But not only does heterosis disappear in F_2, but, in fact, the F_2 hybrids are usually inferior to the parents in viability. Brncic's results are, in a way, even more startling than those of Vetukhiv, for Brncic finds heterosis not only when local populations are hybridized but also when a single intact chromosome of one race is introduced into the genotype of another geographic race. However, when the foreign chromosome is broken up by crossing over in the next generation, the heterosis disappears and there is observed a reduction of the viability.

The work of Vetukhiv and Brncic must be extended to species with different genetic structure before the full implications of this work can be evaluated. In *Drosophila pseudoobscura* and *Drosophila willistoni*, not only the gene pool of a race but even the gene complexes borne in separate chromosomes of that race are adaptively coherent systems forged by natural selection. The breakdown of these systems by recombination results in loss of fitness in F_2 hybrids. On the other hand, heterozygosis for gene alleles is, at least up to a certain point, a viability stimulus. The viability stimulation prevails in the F_1 generation, but it is offset by the breakdown of the integrated gene systems in the F_2 generation.

These results may, at first sight, seem to furnish aid and comfort to the racists, by raising the bugbear of loss of fitness owing to race intermixture. However, any conclusion of this sort would be thoughtless. What has been observed to happen in some strains of two species of Drosophila does not happen in other species. Vetukhiv found no heterosis in F_1 hybrids, and no breakdown in F_2 hybrids, between populations of *Drosophila paulistorum*. The genetic

architecture of the gene pool of a species or a race is a historically evolved characteristic. The matter calls for further exploration, and for the moment generalizations from the existing meager data would be unwise. Yet, the work on the genetic structure of populations of Drosophila has given a glimpse of a vast field of future studies, in which cooperation of geneticists working on human and animal and plant populations is essential. Only after much further work will the true character of the phenomena of integration of the population genotype be learned, and their possible bearing on human problems made clear.

ACKNOWLEDGMENTS

The writers are obligated to their colleagues and friends, Drs. Stan Gartler, J. C. King, Howard Levene, J. A. Moore, C. Pavan, and O. Frota Pessoa for reading and criticizing the manuscript of this article, and for many discussions which have helped to crystallize some of the ideas presented therein.

REFERENCES

BERRY, H. K. 1953. Variations in the urinary excretion pattern in the Texas population. *Amer. Jour. Physical Anthrop.*, 11: 559–575.

BOYD, W. C. 1950. *Genetics and the Races of Man.* Little, Brown. Boston.

BRNCIC, D. 1954. Heterosis and the integration of the genotype in geographic populations of Drosophila pseudoobscura. *Genetics* 39: (in press).

CHETVERIKOV, S. S. 1927. Uber die genetische Beschaffenheit wilder Population. *Verh. V Inter. Kongr. Vererbungaw.*, 2: 1499–1500.

CORDEIRO, A. R., AND DOBZHANSKY, TH., 1954. Combining ability of certain chromosomes in *Drosophila willistoni* and invalidation of the "wild-type" concept. *Amer. Naturalist* 88: 75-88.

DOBZHANSKY, TH. 1951. Human diversity and adaptation. *Cold Spring Harbor Symposia Quant. Biol.*, 15: 385–400.

DOBZHANSKY, TH. AND SPASSKY, B. 1953. Genetics of natural populations. XXI. *Genetics* 38: 471–484.

DOBZHANSKY, TH. AND SPASSKY, B. 1954. Genetics of natural populations. XXII. *Genetics*, 39: (in press).

MULLER, H. T. 1950. Our load of mutations. *Am. J. Human Genet.* 2: 111–176.

PROUT, T. 1952. Selection against heterozygotes for autosomal lethals in natural populations of Drosophila willistoni. *P. N. A. S.* 38: 478–481.

STERN, C., G. CARSON, M. KINST, E. NOVITSKI, AND D. UPHOFF. 1952. The viability of heterozygotes for lethals. *Genetics* 37: 413–449.

VETUKHIV, M. 1953. Viability of hybrids between local populations of Drosophila Pseudoobscura. *P. N. A. S.* 39: 30–34.

WALLACE, B. AND J. C. KING. 1952. A genetic analysis of the adaptive values of populations. *P. N. A. S.* 38: 706–715.

WALLACE, B. AND C. V. MADDEN. 1953. The frequencies of sub- and supervitals in experimental populations of Drosophila melanogaster. *Genetics* 38: 456–470.

WRIGHT, S., DOBZHANSKY, TH., AND HOVANITZ, W. 1942. Genetics of natural populations. VII. *Genetics* 27: 363–394.

Implications of Some Recent Developments in Hematological and Serological Genetics[1]

JAMES V. NEEL

Heredity Clinic, Institute of Human Biology, University of Michigan

THESIS

FOR SOME YEARS NOW two inherited blood disorders, thalassemia and sickle cell anemia, have, because of their apparent sharp restriction to certain groups of people, their relative frequency in these groups, and their deleterious effects, attracted the particular attention of those interested in the population genetics of man. It has appeared that in our thinking about human population genetics, a great gulf should separate the genes responsible for these two diseases from those responsible for certain characteristics thought to be more or less neutral from the standpoint of natural selection, and hence approximating the ideal as genetic indicators of relationship between human populations. With the exception of the Rh locus, the genes responsible for the red blood cell antigens are commonly regarded as outstanding examples of these "neutral" genes. It will be my thesis this afternoon that recent developments, the nature of which will be described, are rapidly narrowing this gulf, and forcing us to consider both kinds of genes in a new light.

THALASSEMIA

Thalassemia is an inherited hematological disorder which occurs in two forms, a severe and a mild, with relatively few intergrades. The severe form of the disease, sometimes called thalassemia major, is characterized by a profound anemia, splenomegaly, the deposition of an iron-containing pigment in the viscera, and hyperplasia of the bone marrow. There are marked morphological abnormalities of the erythrocytes. Death usually occurs before the third decade; reproduction is uncommon. The mild form of the disease, sometimes called thalassemia minor, is characterized by lesser morphological abnormalities of the erythrocytes and only a slight decrease in the amount of hemoglobin present. The genetic relationship between these two forms of thalassemia has been intensively investigated, with results reviewed elsewhere (Chini and Valeri, 1949; Silvestroni and Bianco, 1949; Neel, 1951a; Bianco, Montalenti, Silvestroni, and Siniscalco, 1952). In brief, it appears that the two diseases are

Received March 8, 1954.

[1] Paper read at the Symposium on Genetics and the Races of Man, sponsored by the American Society of Human Genetics, the Genetics Society of America, the Society for the Study of Evolution, and A.A.A.S., Section H-Anthropology, on December 30, 1953.

related as homozygote to heterozygote, i.e., the same gene which is responsible for thalassemia minor when heterozygous produces thalassemia major when homozygous. The considerable range in the expression of both thalassemia major and minor is thought to be due to the action of modifying genes and possibly unrecognized environmental influences. Recently it has been shown that approximately 40 to 60 per cent of the hemoglobin in thalassemia major is of the fetal type (Liquori, 1951; Singer, Chernoff, and Singer, 1951; Rich, 1952, Zannos, 1953), and the biochemical basis of the disease is thought to be an interference with the sequence of reactions leading to normal, adult hemoglobin, with persistence or reactivation of the synthesis of fetal-type hemoglobin (Rich, 1952).

Thalassemia major was first recognized in this country as a clear-cut genetic entity occurring primarily among individuals of Italian or Greek derivation at about the same time that thalassemia minor was independently recognized in Italy (review in Silvestroni and Bianco, 1949; Neel, 1951a). In 1945 Dr. William Valentine and myself reported that among individuals of Italian—largely Sicilian—descent residing in Rochester, New York, the frequency of thalassemia major was approximately 1 in 2400 births, from which we calculated that in this population, as well as Sicily itself, the frequency of thalassemia minor should approximate 1 in 25, i.e., 4 per cent. Survey studies carried out independently in Italy did in fact reveal a frequency of approximately 4 per cent of thalassemia minor in southern Italy and Sicily. The frequency of the gene appeared to fall off sharply as one proceeded northward on the Italian peninsula, until the region of the Po River Valley was reached, where a second concentration of the gene was found, as many as 10 per cent of the residents of one town being reported to show thalassemia minor (Silvestroni and Bianco, 1949).

Thalassemia major has been reported frequently in this country in children of Greek derivation, but no accurate survey figures for the frequency of either the major or minor forms of the disease are available in Greece itself. However, Banton (1951) has reported some very interesting results from the island of Cyprus. Among 495 individuals of Greek extraction residing on the island—largely soldiers and school children—18.8 per cent were said to have thalassemia minor. Among 136 persons of Turkish descent—again predominantly school children and soldiers—21.3 per cent showed thalassemia minor. In one small, isolated village of 80 inhabitants, all Greek Cypriots, 28 of the 65 persons examined were thought to have thalassemia minor, and 3 of them had thalassemia major. However, these figures cannot be taken as representative, since this village was selected for study because the village chief was known to have three sons with thalassemia major, and almost half of the subjects examined were related to the chief.

The available evidence thus suggests that in the northeast quadrant of the

Mediterranean littoral there is a gradient or cline in the frequency of individuals heterozygous for the thalassemia gene, the frequency ranging from approximately 4 per cent in Sicily and southern Italy to 20 per cent in individuals of Turkish extraction of Cyprus, and presumably in Turkey itself. The fragmentary nature of our knowledge is obvious.

Scattered cases of both thalassemia major and minor have been reported in a variety of other racial stocks, e.g., Indians, Filipinos, Negroes, and Chinese (review in Neel, 1951a), but until recently there has been no reason to suspect that the gene frequency in any other region was as high as in Italy, Greece, and Turkey. However, a paper by Minnich, Na-Nakara, Chongchareonsuk, and Kochaseni, which is now in press in BLOOD, and which the authors have kindly permitted me to quote, throws an entirely new light on the distribution of this gene. Out of a total of 367 patients seen between June, 1951, and May, 1952, by the Hematology Service of Siriraj Hospital, Bangkok, Thailand, 46 were found to have an anemia clinically indistinguishable from—and presumbably identical with—thalassemia major. There were limitations on the number of patients who could be accepted for study by the Hematology Service; it is estimated that on the average two or three new patients with the disease were seen each week in the Pediatrics Out-Patient Clinic. The average age of the 32 patients studied in detail was 10.2 years. The patients, by and large, showed striking anemia, the average hemoglobin being 5.1 grams per cent. In view of the early development of severe anemia in this disease, and from what is known of the mortality of untreated thalassemia major as seen in the United States and Italy, it seems reasonable to assume that the patients seen by this Hematology Clinic are the survivors of a much larger group of affected individuals, in terms of frequency at birth. However, even a very approximate estimate of the frequency of the gene in the population is not feasible at the present time, although it is quite possibly the highest yet recognized. Furthermore, there are as yet no studies on the frequency of thalassemia minor. This represents a fertile area for investigation.

As noted above, individuals homozygous for the thalassemia gene seldom reproduce. The problems in selection and mutation posed by the frequency and distribution of thalassemia are obvious.

SICKLE CELL ANEMIA

Sickle cell anemia is a severe, chronic anemia which develops in certain individuals because of the tendency of their erythrocytes to undergo in vivo distortion when subjected to conditions of reduced oxygen tension. This distortion is of several types, but most characteristically consists in the appearance of long filaments extending from the cell. Sickle cells are more rapidly destroyed than normal erythrocytes, in consequence of which a marked anemia may develop. In addition, sickle cells apparently have a tendency to clump together

for mechanical reasons, leading to widespread interference with local blood supply.

In those populations in which sickle cell anemia has been recognized, it has been observed that for each individual who exhibits the anemia there are many more in apparently good health whose erythrocytes can be induced to sickle but who show no ill effects. In these individuals it requires a lower oxygen tension to elicit the sickling, and the distortion of the cells is not usually so bizarre. Such individuals are spoken of as having the sickle cell trait.

Genetic studies carried out over the past several years have shown that the sickle cell trait is due to heterozygosity for a gene which when homozygous produces sickle cell anemia, the genetics of the disease thus being comparable to those of thalassemia (Neel, 1947, 1949, 1951b; Beet, 1949). Sickle cell anemia also results from simultaneous heterozygosity for the sickle cell gene and the genes responsible for thalassemia, hemoglobin C (see below), or hemoglobin D (Itano, 1951). Biochemical studies have indicated that the ultimate basis for the sickling phenomenon is the occurrence of an abnormal type of hemoglobin. In heterozygous individuals, only 25 to 45 per cent of the hemoglobin is abnormal, whereas in homozygotes, 90 to 100 per cent is atypical (Pauling et al., 1949).

The sickling phenomenon was first observed among Negroes in the United States. Subsequent extensive studies have shown that in this country the phenomenon is almost completely confined to that group, with a frequency in the neighborhood of 10 per cent. Studies on the African Negro reveal that in a broad belt extending across roughly the middle third of Africa the frequency of the phenomenon approximates 20 per cent, the frequency varying greatly from tribe to tribe (Lehmann and Raper, 1949), with a rapid decrease in frequency as one proceeds either north or south. The frequency of sickling is very low in the Bushmen and Hottentots, and it seems quite possible that the gene has been introduced into these groups through crossing with the true Negro (review in Neel, 1951a; Hiernaux, 1952, Singer, 1953).

Despite the frequency of the sickling phenomenon in Africa, there was for many years a paucity of case reports of actual sickle cell disease from that continent, the individuals exhibiting the sickling phenomenon appearing with very rare exceptions to have merely the sickle cell trait. One observer went so far as to postulate that the disease in the United States was in some way related to Negro-White admixture (Raper, 1950), a supposed fact which Dr. R. R. Gates (1952) has unfortunately cited as a proven ill effect of miscegenation. Several years ago I drew attention to the very obvious alternative, that the disease in Africa does have the frequency at birth which the frequency of the sickling phenomenon would suggest, but that "because of the more rigorous conditions obtaining in the early years of life there, most of the (affected) children are eliminated when quite young, either in consequence of a hemolytic

crisis or because of intercurrent disease" (Neel, 1951a). Shortly thereafter, reports from Africa, especially the Congo region, established the fact that when the disease is sought for at the pediatric age level, it is to be found with a considerable frequency, a frequency which may in fact match that demanded by the homozygous-heterozygous theory. (Lambotte-Legrand and Lambotte-Legrand, 1951; Foy and Kondi, 1951; Foy, Kondi, and Hargreaves, 1952; Vandepitte, 1952; Edington, 1953).

From time to time there have appeared in the literature reports of the sickling phenomenon in presumably Caucasian individuals. In most instances the individuals involved have been of Italian or Greek derivation, and the frequency of the findings has been so low that presumably it could be explained by Negro admixture at some remote time. However, two systematic studies of recent years have forced us to extend our concept of the distribution of the sickle cell gene. The first of these observations has to do with reports that in certain cities and villages in Greece a high proportion of the inhabitants exhibit the sickling phenomenon. Thus, Choremis et al. in 1951 estimated that in villages situated around Lake Copais a minimum of 0.25 per cent of the children suffer from sickle cell anemia, this observation implying a frequency of the sickle cell trait equal to that in the American Negro. Although the published figures of these investigators left no doubt that they observed the sickling phenomenon, their clinical data, as Lehmann (1951) has pointed out, did not permit one to be certain whether they were dealing with the sickle cell trait or sickle cell anemia, or, if with sickle cell anemia, whether this is the type now known to result from simultaneous heterozygosity for the sickling and thalassemia genes. However, more recent studies by this same group (Choremis, et al., 1953) revealed 17.7 per cent sickling in a small sample of 102 persons from this area, a finding consistent with the above mentioned estimate concerning the frequency of sickle cell anemia. The frequency of the *cDe* (R^o) chromosome in this group was only 4.6 per cent. This may be taken as evidence against the introduction of the gene by Negro admixture. Caminopetros in 1952 reported that 49.1 per cent of a sample of 116 residents of Athens, originally from different areas of the Greek mainland and islands, exhibited the sickling phenomenon. Choremis et al. (1953) were unable to corroborate this report, and suggest that Caminopetros' technique produced a type of cell distortion which he confused with true sickling. At the moment, then, only the one focus of the sickling phenomenon in Greece is established. Further data from this country are awaited with interest.

The second extensive set of observations on the occurrence of sickling in non-Negroes concerns the Dravidian-speaking Veddoids of southern India. Lehmann and Cutbush (1952a, b) have reported that 31.3 per cent of 201 individuals tested from three tribes exhibited the sickling phenomenon. Sickling was also found, although in a much lower frequency, in two neighboring Indid

tribes but was not present in four other Indid tribes. The question immediately arises as to the anthropological relationship of these Dravidians to the African Negro. There are certain gross physical similarities between the two groups (Haddon, 1925). Much more critical evidence concerning their relationship comes from the serological studies of Lehmann and Cutbush (1952b). The R^o (*cDe*) gene, which because of its high frequency in the African Negro is thought of as a "Negroid" trait, was not observed in any of the 156 Veddoids tested. Furthermore, 14 of the 156 Veddoids tested showed the rare R^z (*CDE*) gene, known to be very uncommon except in bloods from Siam, Australasia, and America. These findings, like those on the Greeks, permit of two alternate interpretations, namely, (1) that the gene responsible for the sickling phenomenon has been transmitted to both groups by a common ancestor (Lehmann, 1952; Mourant, 1952), or (2) that the sickling gene (or another gene with the same effect) has originated independently in the African Negro and the Indian groups in question (Mourant, 1952). The description of three cases of sickle cell anemia among children of laborers in the Upper Assam tea plantations (Dunlop and Mozumder, 1952) raises the possibility of multiple foci of the sickling phenomenon in India.

Because of certain physical similarities between the Veddoids and the Australian aborigines, as well as important similarities in their blood groups (Lehmann and Cutbush, 1952b; Simmons and Graydon, 1948; Sanger, Walsh and Kay, 1951), Horsfall and Lehmann (1953) and Simmons, Graydon, and Birdsell (1953) have recently extended the search for the sickling phenomenon to the Australia aborigines, but found no individuals with the sickle cell trait among a total of 197 persons tested. Lehmann and Ikin (in press), as quoted by Horsfall and Lehmann (1953), also found no sickling among 68 Andamanese Negritos.

Whether yet other foci of the sickling phenomenon will be discovered remains to be seen. At the very least, these recent discoveries force us to reconsider the concept of the restricted distribution of the sickling gene, just as we have been forced to reconsider on the geography of thalassemia.

Again, the problem in gene dynamics is a fascinating and perplexing one. What factor or combination of factors maintains a gene with such deleterious effects when homozygous at so high a frequency?

HEMOGLOBIN C

As a rule, both parents of a child with sickle cell anemia exhibit the sickle cell trait; indeed, this observation was an important link in the chain of evidence responsible for the above-described theory of the genetics of this anemia. Occasional exceptions to this rule are encountered, in the form of families in which only one parent of a child with what seems to be sickle cell anemia will exhibit the sickle cell trait. The intensive study of such families by ourselves

and others has led to the discovery of three additional genetic backgrounds (listed on page 211) which may be responsible for the development of sickle cell anemia. One in particular deserves consideration in connection with this Symposium. It has now been shown that in the majority of the exceptional families thus far discovered, the nonsickling parent possesses an abnormal type of hemoglobin, termed hemoglobin C because it was the third type of hemoglobin to be recognized. Its presence is apparently due to a single gene. Children who inherit this gene from one parent and a sickle cell gene from the other parent develop a type of sickle cell anemia, distinguished clinically from the classical form by its milder course (summary in Neel, Kaplan, and Zuelzer, 1953; Kaplan, Zuelzer, and Neel, 1953). The genetic relationship of the genes responsible for the sickling phenomenon and for hemoglobin C is unknown. Itano (1953) has suggested that the two genes may be members of a multiple allelic series, but critical evidence is lacking.

The positive identification of hemoglobin C depends upon certain laboratory methods such as the techniques of electrophoresis. This makes studies on its racial distribution somewhat more laborious than studies on thalassemia or the sickling phenomenon. However, the recent applications of paper electrophoresis to the identification of abnormal hemoglobins makes possible surveys which would be prohibitively time consuming with the classical Tiselius apparatus. Smith and Conley (1953) have now shown that in a series of 500 American Negroes, of whom 8.2 per cent exhibited the sickling phenomenon, 2 per cent gave a positive test for hemoglobin C. None of 500 Caucasians tested was found to exhibit the sickling phenomenon or to possess hemoglobin C. In an unpublished series of observations carried out in collaboration with Dr. W. W. Zuelzer and Mr. James Gallacher, utilizing a modification of paper electrophoresis which permits the simultaneous analysis of as many as 50 bloods, we have found 1.4 per cent of a series of 209 blood samples from American Negroes, and 0 per cent of 72 blood samples from Caucasians, to contain hemoglobin C.

Hemoglobin C would thus appear to be another inherited characteristic exhibiting frequency differences from one population group to the next. Obviously the study of the distribution of this trait is not even well begun. Assuming for the moment that the average American Negro is approximately ⅓ Caucasian and Indian in ancestry, and assuming further that the gene responsible for hemoglobin C is not present in Caucasians and Indians, then we may estimate that in those parts of Africa which are the provenience of the American Negro, the hemoglobin C trait will be found in about 3 per cent of all persons. What fragmentary knowledge now exists indicates that persons homozygous for the hemoglobin C gene exhibit only minor hematological abnormalities (Levin, Schneider, Cudd, and Johnson, 1953; Ranney, Larson, and McCormack, 1953; Spaet, Alway, and Ward, 1953. Individuals heterozygous for both the sickle cell and hemoglobin C genes are more seriously handi-

capped. The fact that such an interaction occurs, regardless of whether the two genes are alleles or occupy independent loci, increases the selection pressure against the sickle cell gene and still further intensifies the problems posed by its high frequency.

THE RESTRICTED DISTRIBUTION OF SOME OF THE GENES RESPONSIBLE FOR SEROLOGICAL REACTIONS

Although, as is well known, wide variations have been observed from population to population as regards the frequency of some of the genes responsible for serological reactions, it is uncommon for a serological reaction to show as apparently sharp a geographical restriction as the three traits so far discussed. Nevertheless, there are certain instances where this appears to be true. The failure to detect either the A_2 or the S gene of the *MNSs* complex in certain groups is well known. As additional examples, one might cite the work of Landsteiner, Strutton, and Chase (1934), who produced by the immunization of rabbits with blood from an American Negro an antiserum which agglutinated the cells of 14 out of 191 American Negroes, but only 2 out of 387 white persons. More recently, Chalmers, Ikin, and Mourant (1953) have reported that the antigen in question, known as the Hunter factor, and apparently due to a single gene, was present in 21.7 per cent of a sample of 138 West Africans. These same workers found that the Henshaw antigen, originally described by Ikin and Mourant (1951) and also apparently due to a single gene, was present in 2.7 per cent of 1,428 West Africans but completely lacking in 1,500 Europeans. A final example of a red blood cell antigen of restricted distribution has recently been provided by Wiener, Unger, and Gordon (1953), who, on the basis of a hemolytic transfusion reaction occurring in an American Negro, recognized a new blood factor, U, present in every one of 690 Caucasoids tested and in 421 of 425 Negroids in the United States. Although genetic studies are lacking, the four Negroids lacking the antigen presumably resemble the original patient in their homozygosity for an uncommon gene. The similarity of the frequency of the less common gene in both the Henshaw and U antigenic systems to the probable frequency of the gene responsible for hemoglobin C raises an obvious question of relationship. The fact that all three of the examples just cited of antigens largely or entirely restricted to one ethnic group involve the Negro can scarcely in the present state of our knowledge be taken to indicate that such antigens are especially prevalent in this group, since many other ethnic groups have not been studied to the same extent.

RECENT DATA CONCERNING THE OPERATION OF SELECTIVE FACTORS WITH REFERENCE TO GENES RESPONSIBLE FOR SEROLOGICAL REACTIONS

Thus far my remarks have been directed toward the proposition that the genes responsible for certain hematological abnormalities may have a wider

distribution than was felt to be the case a few years ago. This is certainly true for the genes responsible for thalassemia and the sickling phenomenon; the discovery of hemoglobin C is still too recent for the necessary data to have become available. I would like now to pick up the second thread of my argument, namely, that the genes responsible for a variety of allegedly more or less neutral traits may be more subject to selective factors than is commonly thought. In particular, I have reference to the genes responsible for the red blood cell antigens. Time permits only a rather cursory review of the evidence.

The A-B-O genes

We will consider first the well known A-B-O reactions. The impression is certainly widespread that aside from transfusion problems these reactions are of little physiological significance and that the genes responsible for these reactions approach the ideal as "neutral" indicators of anthropological relationships. The evidence that this may not be the case falls into two categories, statistical and medical.

a. *Statistical evidence.* This type of evidence is concerned with the demonstration that individuals with specified blood groups are represented in excess over random expectation under conditions which imply a differential mortality or morbidity. Hirszfeld and Zborowski in 1925 first raised the possibility that in marriages of A × O individuals, the incidence of A children was lower when it was the mother who was the O parent than when she was A. In 1947 Waterhouse and Hogben surveyed the pertinent literature on this point, and concluded that there was a highly significant deficiency of A children from marriages of O mothers and A fathers, this deficiency amounting to about 25 per cent. This would represent a fetal death rate of 8 per cent of A children, or 3 per cent of all conceptions. These conclusions, which if correct indicate the highest order of selection recognized for any single genetic locus in man, will be challenged in an article by Brandt and Bennett, to appear in a forthcoming number of the *Annals of Eugenics*, and which I have kindly been permitted to quote. These investigators question the validity of the statistical methods employed by Waterhouse and Hogben. They find evidence of heterogeneity among the various sets of observations pooled for the analysis, and conclude from their own analysis that the present data are inadequate to permit definite conclusions on this point. On the other hand, Kirk, Kirk, and Stenhouse (1953), in a search for a mechanism which might maintain the constancy of the A-B-O blood groups in the face of the selection described by Waterhouse and Hogben (1947), have observed differences in the average number of pregnancies with age between women of group O and A. These investigators suggest that the most likely means of compensation for the pregnancy loss of A-O incompatible matings is that women of group O in a compatible mating group are on the average more fertile than either women of group O in an incompatible mating

group or women of group A. The possible complexity of the situation is underlined by the report by Sanghvi (1951) that the percentage of male births is significantly less among A babies born to A mothers than among O infants born to O mothers or B infants to B mothers.

From time to time there have appeared suggestions that individuals of particular A-B-O types might have increased susceptibilities to certain diseases (review in Mayo and Fergeson, 1953). Two recent papers are of particular interest in this respect. Aird, Bentall, and Roberts (1953) report that among patients hospitalized in a number of cities in England and Scotland because of cancer of the stomach, the frequency of blood group A is greater and the frequency of blood group O less than the frequencies in the general population of the same localities. Thus, in Scotland among patients with gastric carcinoma 36.4 per cent were group A, as contrasted with 32.5 per cent group A among the controls; in northern England the figures were 46.4 and 39.3 per cent; and in London, 46.0 and 42.2 per cent. It is not clear whether this finding implies a causal relationship of the blood group A gene to gastric carcinoma, or whether a subgroup of the population with an increased susceptibility to gastric carcinoma also has a higher frequency of the A gene. In any event, since only about 5 per cent of all stomach cancers develop in individuals below the age of 45 (i.e., in the age of reproduction), the differential selection, while statistically significant, would appear to be small. A second recent paper on the question of A-B-O types and disease susceptibility is by Hunt and Lucia (1953), who have reported a relative increase in the frequency of blood group O among patients found to have an acute hemolytic anemia. Again, a cause and effect relationship is not established. To what extent these reports will stand the test of time remains to be seen.

b. *Clinical evidence.* There is also growing evidence from the clinical side that maternal-fetal incompatibility with respect to the *A-B-O* genes may result in a selective infant morbidity and mortality. That such incompatibility may be responsible for hemolytic disease seems no longer in doubt, although for technical reasons the demonstration in any individual case is more difficult than when Rh incompatibility is the cause of the disease [summaries in Mollison (1951) and Levine, Vogel, and Rosenfield (1953)]. From 5 to 20 per cent of all cases of hemolytic disease of the newborn has been attributed to A-B-O incompatibility, the remaining 80–95 per cent of the cases being due, with a few exceptions to be mentioned later, to Rh incompatibility. From the estimate that hemolytic disease due to Rh incompatibility has a frequency of between 1 in 150 and 1 in 200 (see below) it follows that very roughly 1 in 2000 newborn infants suffers from the effects of maternal-fetal A-B-O incompatibility. This would represent a significant type of selection. However, attempts to place this observation in its proper perspective from the standpoint of natural selection are complicated by the suggestion of Crawford et al. (1952) that the formation

of immune A isoantibodies—presumed to play a role in the hemolytic disease—may be increased by such heterogenetic stimuli of our times as tetanus and diphtheria antitoxin and "triple typhoid" vaccine. Whether these stimuli are more effective than the diseases they have replaced remains to be determined.

The M-N-S reactions

Evidence that the M-N-S system may be the object of selective forces is again of two types, statistical and clinical. On the statistical side is the finding, summarized by Taylor and Prior (1939) and Wiener (1943), of an excess of MN children among the offspring of MN × MN matings. The interpretation of this finding remains a moot point, Taylor and Prior (1939) believing that it is a real phenomenon, but Wiener (1943) attributing it to technical errors. Cotterman (personal communication) has pointed out that these results might be explained by the occurrence of a rare gene responsible for both the M and N reactions. On the clinical side there is evidence that occasionally an anti-S agglutinin may develop during pregnancy, with possibly deleterious effects on the fetus (Sanger, Race, Walsh, and Montgomery, 1948; Pickles, 1948; Levine, Ferraro, and Koch, 1952).

The Rh reactions

The evidence that maternal-fetal incompatibility with respect to the Rh genes results in disease and death in the newborn is so well known as to require no review here. In the United States approximately 1 in each 500 to 1000 infants exhibits severe hemolytic disease or even dies in consequence of Rh incompatibility. An additional number of infants may exhibit milder Rh disease. Levine, Vogel, and Rosenfield, in their authoritative review (1953), accept the figure that in all its forms, Rh hemolytic disease occurs in a population with about 15 per cent Rh negative individuals (the U.S. frequencies) in 1 out of 150 to 1 in 200 of all full-term pregnancies. This estimate represents a minimum index of the amount of selection involving the Rh system. Even so, the apparent magnitude of the selection involved is, in the terms of the population geneticist, very considerable, suggesting an "unstable" system. Wiener (1942) and Haldane (1942) were quick to recognize this, the latter pointing out three alternative explanations of the findings, namely, that 1) recent environmental changes have altered for the worse the biological consequences of maternal-fetal Rh incompatibility, 2) the selection against Rh heterozygotes is balanced by a type of counter selection yet to be discovered, or 3) the present genetical situation is of recent origin and probably due to racial mixture.

In the absence of evidence for either 1) or 2), both Haldane and Wiener appear to incline towards the third possibility. While this appears to present a solution of the immediate dilemma, we are then confronted with the even more perplexing problem of the origin of an Rh-positive and an Rh-negative race.

Spencer (1947) has added a fourth type of explanation to the list, which avoids this last question, namely, that 4) the situation can be explained by a combination of differential rates of mutation for the *Rh* genes ($Rh \rightarrow rh > rh \rightarrow Rh$), genetic drift, and reproductive compensation for the death of children in consequence of Rh incompatibility. However, Li (1953) has recently demonstrated mathematically that reproductive compensation cannot lead to a stable equilibrium value for *Rh* gene frequencies. Obviously no decision concerning the relative validity of these various explanations is possible at present.

Studies on the circumstances under which Rh isoimmunization occurs have provided one insight into the possible complexity of the selective factors responsible for present day gene frequencies. Levine in 1943 first drew attention to the fact that the mothers of children with hemolytic disease due to the Rh antibodies were more often compatibly mated with respect to the A-B-O system than were a random series of husbands and wives (review in van Loghem and Spaander, 1948; Wiener, Nappi, and Gordon, 1953). The term "compatible mating" as here used refers to one in which the husband could be a blood donor to his wife from the A-B-O standpoint. It would appear that the strength of the selection to which the *Rh* genes are subject is not independent of A-B-O frequencies.

Other inherited serological traits.

There are now recognized approximately a dozen other inherited serological antigens. Several of these antigens (Kell, Duffy, Kidd, etc.) have been shown to be possibly associated with hemolytic disease of the newborn (review in Race and Sanger, 1951; Levine, Vogel, and Rosenfield, 1953), so that a type of selection may be presumed to be at work, but the exact magnitude of this selection cannot now be specified. In view of the evidence that Rh and A-B-O incompatibility account for the vast majority of hemolytic disease, it may be presumed to be small from this standpoint.

From this very cursory review, it is apparent that some of the genes responsible for certain serological reactions may be the object of selective forces of the same order of magnitude as those to which the thalassemia and sickle cell genes are subjected. It is an interesting commentary that despite all the work done on the A-B-O system, our knowledge of its true biological significance should be so fragmentary. The fact is that our approach to the problem in the past has permitted us to recognize only the very grossest types of selection. Perhaps the time has now come for a concerted attack on the biological significance of so well studied a group as the A-B-O system.

CONCLUDING REMARKS

I should like to return now to the thesis laid down in my opening sentences. This is to the effect that in the light of our expanding knowledge of the genetics

of man, there are decreasing grounds for regarding the genes responsible for thalassemia and the sickling phenomenon as genetic curiosities, clearly set apart from the more respectable genes responsible for the serological reactions. Some of the genes responsible for serological reactions are distributed among those of the earth's inhabitants so far studied in almost as spotty a fashion as the thalassemia and sickle cell genes. Furthermore, it now appears that selection may be laying almost as heavy a hand on certain of the "serological genes" as on the genes responsible for these two anemias. It is important that we recognize the unity of problem involved here. I do not mean to imply that the same interplay of mutation and selection found to explain one gene frequency can be carried over like a blanket to another gene of comparable frequency. But in what appears to be a continuous spectrum of mutation-selection effects, an explanation valid for one may provide an insight into the other. I have recently reviewed elsewhere our present unsatisfactory knowledge concerning mutation and selection with respect to the sickle cell locus (Neel, 1953). The factors responsible for the frequencies of the "serological genes" are every bit as unknown as those responsible for the frequencies of the thalassemia and sickle cell genes. In our approach to unraveling the selection-mutation-genetic drift tangle, I suggest that while we neglect no approach, we devote particular attention to the mutation end of the knot. The clear demonstation of genetic drift depends on repeated samplings in time of the frequency of a "neutral" gene in a specified population. But it is now apparent that the evidence for neutrality is negative evidence, with all the drawbacks of that type of data. Furthermore, although it is of course possible to observe as many as three generations at any one point in time, ideally each generation should be examined shortly after birth, in order to obviate selection effects. Selective factors are changing so rapidly that except where lethality or near lethality is involved, today's findings may throw little light on yesterday's facts. On the other hand, particularly with modern methods of paternity exclusion, mutation rate studies employing the "direct" method, even with all their recognized drawbacks (cf. Neel, 1952), appear to emerge as the approach most capable at the present time of providing immediate insight into certain present day gene frequencies.

REFERENCES

AIRD, I., BENTALL, H. H., AND ROBERTS, J. A. F., 1953. Relationship between cancer of stomach and ABO blood groups. *Brit. Med. J.*, 1: 799–801.

BANTON, A. H., 1951. A genetic study of Mediterranean anaemia in Cyprus. *Am. J. Human Genet.*, 3: 47–64.

BEET, E. A., 1949. The genetics of the sickle cell trait in a Bantu tribe. *Ann. Eug.*, 14: 279–284.

BIANCO, I., MONTALENTI, G., SILVESTRONI, E., AND SINISCALCO, M., 1952. Further data on genetics of microcythaemia or thalassaemia minor and Cooley's disease or thalassaemia major. *Ann. Eug.*, 16: 299–315.

BRANDT, J., AND BENNETT, J. H. Some more exact tests of significance for O-A maternal-fetal incompatibility. *Ann. Eug.*, in press.

CAMINOPETROS, J., 1952. Sickle cell anomaly as sign of Mediterranean anemia. *Lancet* 1: 687–693.

CHALMERS, J. N. M., IKIN, E. W., AND MOURANT, A. E., 1953. A study of two unusual blood group antigens in West Africans. *Brit. Med. J.*, 2: 175–177.

CHINI, V., AND VALERI, C. M., 1949. Mediterranean hemopathic syndromes. *Blood* 4: 989–1013.

CHOREMIS, C., ZERVOS, N., CONSTANTINIDES, V., AND ZANNOS, L., 1951. Sickle-cell anaemia in Greece. *Lancet*, 1: 1147–1149.

CHOREMIS, C., IKIN, E. W., LEHMANN, H., MOURANT, A. E., AND ZANNOS, L., 1953. Sickle-cell trait and blood groups in Greece. *Lancet*, 265: 909–911.

CRAWFORD, H., FALCONER, H., CUTBUSH, M., AND MOLLISON, P. L., 1952. Formation of immune A isoantibodies with special reference to heterogenetic stimuli. *Lancet*, 2: 219–223.

DUNLOP, K. J., AND MOZUMDER, U. K., 1952. The occurrence of sickle cell anaemia among a group of tea garden labourers in Upper Assam. *Ind. Med. Gaz.*, 87: 387–391.

EDINGTON, G. M., 1953. Sickle-cell anaemia in Accra district of Gold Coast. *Brit. Med. J.*, Oct. 31, p. 957–961.

FOY, H., AND KONDI, A., 1951. Sickle-cell anaemia in Africans. *Lancet*, 2: 451–452.

FOY, H., KONDI, A., AND HARGREAVES, A., 1952. Anaemias of Africans. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 46: 327–358.

GATES, R. R., 1952. Disadvantages of race mixture. *Nature*, 170: 896.

HADDON, A. C., 1925. *The Races of Man.* New York: Macmillan Co., 201 pp.

HALDANE, J. B. S., 1942. Selection against heterozygosis in man. *Ann. Eug.*, 11: 333–540.

HIERNAUX, J., 1952. La génétique de las sicklémie et l'intérêt anthropologique de sa fréquence en Afrique noire. *Ann. du Musée Royal du Congo Belge*, Série in 8°, v. 2.

HIRSZFELD, L., AND ZBOROWSKI, H., 1925. Gruppenspezifische Beziehungen zwischen Mutter undo Frucht und elektive Durchlassigkeit der Placenta. *Klin. Wschr.*, 4: 1152–1157.

HUNT, M. L., AND LUCIA, S. P., 1953. The occurrence of acquired hemolytic anemia in subjects of blood group O. *Science*, 118: 183–184.

IKIN, E. W., AND MOURANT, A. E., 1951. A rare blood group antigen occurring in Negroes. *Brit. Med. J.*, 1: 456–457.

ITANO, H. A., 1951. A third abnormal hemoglobin associated with hereditary hemolytic anemia. *Proc. Nat. Acad. Sci.*, 37: 775–784.

ITANO, H. A., 1953. Human hemoglobin. *Science*, 117: 89–94.

KAPLAN, E., ZUELZER, W. W., AND NEEL, J. V., 1953. Further studies on hemoglobin C. II. The hematologic effects of hemoglobin C alone and in combination with sickle cell hemoglobin. *Blood*, 8: 735–746.

KIRK, R. L., KIRK, M., AND STENHOUSE, N. S., 1953. Differential fertility between women of blood groups O and A. *Brit. J. Prev. & Soc. Med.*, 7: 1–8.

LAMBOTTE-LEGRAND, J., AND LAMBOTTE-LEGRAND, C., 1951. L'anémie a hématies falciformes chez l'infant indigène du Bas-Congo. *Mémoirs Institut Royal Colonial Belge*, v. 19.

LANDSTEINER, K., STRUTTON, W. R., AND CHASE, M. W., 1934. Agglutination reaction observed with some human bloods, chiefly among Negroes. *J. Immunol.*, 27: 469–472.

LEHMANN, H., 1931. Sickle cell anemia in Greece. *Lancet*, 1: 1279.

LEHMANN, H., AND CUTBUSH, M., 1952a. Sickle-cell trait in southern India. *Brit. Med. J.*, 1: 404.

LEHMANN, H., AND CUTBUSH, M., 1952b. Sub-division of some southern Indian communities

according to the incidence of sickle-cell trait and blood groups. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 46: 380–383.

LEHMANN, H., AND RAPER, A. B., 1949. Distribution of the sickle-cell trait in Uganda, and its ethnological significance. *Nature*, Lond., 164: 494.

LEVIN, W. C., SCHNEIDER, R. G., CUDD, J. A., AND JOHNSON, J. E., 1953. A family with homozygous hemoglobin C and sickle cell trait union: a clinical, hematological and electrophoretic study. *Proc. Central Soc. Clin. Res.*, 26: 64–65.

LEVINE, P., 1943. Serological factors as possible causes in spontaneous abortions. *J. Hered.*, 34: 71–80.

LEVINE, P., FERRARO, L. R., AND KOCH, E., 1952. Hemolytic disease of the newborn due to anti-S. *Blood*, 7: 1030–1037.

LEVINE, P., VOGEL, P., AND ROSENFIELD, R. E., 1953. Hemolytic disease of the newborn. *Advances in Pediatrics*, 6: 97–156.

LI, C. C., 1953. Is Rh facing a crossroad? A critique of the compensation effect. *Amer. Nat.*, 87: 257–261.

LIQUORI, A. M., 1951. Presence of fetal hemoglobin in Cooley's anemia. *Nature*, 167: 950–951.

MAYO, C. W., AND FERGESON, J. O., 1953. Are certain diseases associated with specific blood groups or Rh antigens? *Arch. Surg.*, 66: 406–409.

MINNICH, V., NA-NAKARA, S., CHONGCHAREONSUK, S., AND KOCHASENI, S. Mediterranean anemia: a study of thirty-two cases in Thailand. *Blood*, in press.

MOLLISON, P. L., 1951. *Blood Transfusions in Clinical Medicine.* Oxford: Blackwell Scientific Publications, 456 pp.

NEEL, J. V., 1947. The clinical detection of the genetic carriers of inherited disease. *Med.*, 26: 115–153.

NEEL, J. V., 1949. The inheritance of sickle cell anemia. *Science*, 110: 64–66.

NEEL, J. V., 1951a. The population genetics of two inherited blood dyscrasias in man. *Cold Spring Harbor Symp. in Quant. Biol.*, vol. 15: 141–158.

NEEL, J. V., 1951b. The inheritance of the sickling phenomenon, with particular reference to sickle cell disease. *Blood*, 6: 389–412.

NEEL, J. V., 1952. The study of human mutation rates. *Amer. Nat.*, 86: 129–144.

NEEL, J. V., 1953. Data pertaining to the population dynamics of sickle cell disease. Am. J. Human Genet., 5: 154–167.

NEEL, J. V., KAPLAN, E., AND ZUELZER, W. W., 1953. Further studies on hemoglobin C. I. A description of three additional families segregating for hemoglobin C and sickle cell hemoglobin. *Blood*, 8: 724–734.

NEEL, J. V., AND VALENTINE, W. N., 1945. The frequency of thalassemia. *Am. J. Med. Sci.*, 209: 568–572.

PAULING, L., ITANO, H. A., SINGER, S. J., AND WELLS, I. C., 1949. Sickle cell anemia, a molecular disease. *Science*, 110:543–548.

PICKLES, M. M., 1948. A further example of the anti-S agglutinin. *Nature*, 162: 66.

RACE, R. R., AND SANGER, R., 1950. *Blood Groups in Man.* Oxford: Blackwell Scientific Publications, 290 pp.

RANNEY, H. M., LARSON, D. L., AND MCCORMACK, G. H., JR. Some clinical, biochemical, and genetic observations on hemoglobin C. *J. Clin. Invest.* 32: 1277–1284.

RAPER, A. B., 1950. Sickle-cell disease in Africa and America—a comparison. *J. Trop. Med.*, 53: 49–53.

RICH, A., 1952. Studies on the hemoglobin of Cooley's anemia and Cooley's trait. *Proc. Nat Acad. Sci.*, 38: 187–196.

SANGER, R., RACE, R. R., WALSH, R. J., AND MONTGOMERY, C., 1948. An antibody which subdivides the human MN blood groups. *Heredity*, 2: 131–139.

SANGHVI, L. D., 1951. ABO blood groups and sex ratio at birth in man. *Nature*, 168: 1077.

SILVERSTRONI, E., AND BIANCO, I., 1949. Microcytemia, constitutional microcytic anemia, and Cooley's anemia. *Am. J. Human Genet.*, 1: 83–93.

SIMMONS, R. T., GRAYDON, J. J., AND BIRDSELL, J. B., 1953. High R^2 frequency in the blood of Australian aborigines. *Nature*, 172: 500.

SINGER, K., CHERNOFF, A. I., AND SINGER, L., 1951. Studies on abnormal hemoglobins. I and II. *Blood*, 6: 413–435.

SINGER, R., 1953. The sickle cell trait in Africa. *Amer. Anthrop.*, 55: 634–648.

SMITH, E. W., AND CONLEY, C. L., 1953. Filter paper electrophoresis of human hemoglobins with special reference to the incidence and clinical significance of hemoglobin C. *Bull. Johns Hopkins Hosp.*, 93: 94–106.

SPAET, T. H., ALWAY, R. H., AND WARD, G., 1953. Homozygous type "C" hemoglobin *Pediatrics*, 12: 483–490.

SPENCER, W. P., 1947. On Rh gene frequencies. *Amer. Nat.*, 81: 237–240.

TAYLOR, G. L., AND PRIOR, A. M., 1939. Blood groups in England. III. Discussion of the family material. *Ann. Eug.*, 9: 18–44.

VANDEPITTE, J. M., 1952. Sickle-cell anaemia in Africa. *Brit. Med. J.*, 1: 920.

VAN LOGHEM, J. J., AND SPAANDER, J., 1948. L'influence de l'incompatibilité du système ABO sur l'antagonisme Rh. *Rev. d'Hém.*, 3: 276–286.

WATERHOUSE, J. A. H., AND HOGBEN, L., 1947. Incompatibility of mother and foetus with respect to the iso-agglutinogen A and its antibody. *Brit. J. Social Med.*, 1: 17.

WIENER, A. S., 1942. The Rh factor and racial origins. *Science* 96: 407–408.

WIENER, A. S., 1943. *Blood Groups and Transfusion*, 3rd ed. Springfield, Ill.: Charles C. Thomas, pp. 438.

WIENER, A. S., NAPPI, R., AND GORDON, E. B., 1953. Studies in Rh sensitization. VI. A-B-O blood groups and Rh subtypes in sensitized and non-sensitized Rh-negative pregnant women. *Blood*, 8: 1024–1028.

WIENER, A. S., UNGER, L. J., AND GORDON, E. B., 1953. Fatal hemolytic transfusion reaction caused by sensitization to a new blood factor U. *J.A.M.A.*, 153: 1444–1446.

ZANNOS, L., 1953. Studies on the resistance of haemoglobin to alkali. *Acta Ped.*, 42: 305–312.

Blood Factor Incompatibility in the Etiology of Mental Deficiency[1]

EMANUEL HACKEL[2]

Department of Natural Science,[3] The Basic College, Michigan State College, East Lansing, Michigan

THE ROLE OF BLOOD GROUP INCOMPATIBILITY between mother and child in the etiology of mental deficiency has been the subject of speculation for many years. Even before the discovery of the Rh group of antigens, various hypotheses were advanced regarding ABO group incompatibility as a causative agent of mentally deficient progeny. Hemolytic disease of the newborn (or of the fetus) has been known for many years. Orth in 1875 and later Schmorl in 1904 related hemolytic disease to prenatal damage to the brain. Later workers showed a higher incidence of mental deficiency among children who had suffered severe jaundice at birth than is found in the general population. This severe jaundice indicates affliction with hemolytic disease, which in turn suggests blood group incompatibility in the mother-child pair.

The discovery of the Rh series of antigens was instrumental in explaining the phenomenon of hemolytic disease in ABO compatible mother-child pairs. Furthermore, it is well known that hemolytic disease may, through damage to the brain tissue, cause mental deficiency.

The role of blood group incompatibility, in the absence of any known hemolytic disease, as an etiological agent for mental deficiency has been investigated several times, with no universal agreement among the investigators. Yannett and Liebermann (1944) were the first to report a statistical study in which a significant increase in Rh negative mothers of mentally deficient children occurred. Snyder, Schonfeld, and Offerman (1945a, 1945b) reported findings substantially in agreement with those of Yannett and Liebermann (1944). In another report, Yannett and Liebermann (1946) confirmed their earlier findings.

Cappell (1947), Böök et al. (1949), Gilmour (1950) and Zwerling et al. (1951) all report findings which disagree with those mentioned earlier. In all of these investigations, save that of Zwerling et al. only the *D* factor of the Rh series

Received September 6, 1953.

[1] This study was supported by research grants from the New Land Foundation, the M.S.C. (Alumni) Fund, the Michigan State College All-College Research Fund, the Michigan Department of Mental Health and the Biology Fellowship Fund at M.S.C.

[2] Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Graduate Studies, Department of Zoology, Michigan State College, East Lansing, Michigan.

[3] Contribution No. 63.

was investigated. Zwerling et al. examined their samples for the *D*, *C*, *E* and *c* factors. Thus it seems that while the early investigations showed a positive correlation between mother-child incompatibility and mental deficiency, the more recent papers do not confirm this finding.

METHOD

Blood samples from 980 mentally deficient patients at three Michigan state institutions (Lapeer State Home and Training School, Coldwater State Home and Training School and Mt. Pleasant State Home and Training School) were examined for the ABO and Rh antigens. (The Rh tests were for the *D*, *C*, *E*, *c*, *e* and D^u factors.) Samples were also obtained from mothers of 278 of the patients, so that 278 mother-child pairs were able to be studied. This report is concerned with these mother-child pairs; the data for the group of mental defectives will be reported later.

The patients were divided into three groups: (1) those for whom a diagnosis of a specific etiology existed; (2) those for whom a diagnosis of a specific etiology was lacking; and (3) those cases diagnosed as mongoloids. (These were placed in a separate category since this diagnosis does not fit clearly into either of the other groups.) In each case, the diagnosis was obtained from the official records at the institution in which the patient resided.

Table 1 shows the sex distribution of the patients in the three groups.

Samples of three to five ml. of whole blood were taken from the subjects by venipuncture. Blood samples of patients and mothers were typed and compared. Standard techniques using serums prepared by the Ortho Pharmaceutical Corporation were employed in typing. Any factor present in the patient, but absent in the mother was considered to be incompatible.

Statistical analyses of the data were made. The observed and expected values were compared by applying the chi-square test of goodness of fit after Fisher (1948). The methods used in the statistical analyses follow the recommendations of Cochran (1952) and Katz (1953). In some cases, expected values of less than five appear. As Cochran (1952) points out, this is an arbitrarily chosen value; and rigid adherence to it would have necessitated excessive pooling of classes with the subsequent loss of sensitivity of the test. It was felt, therefore, that the results would be more meaningful and the power of the test increased

TABLE 1. SEX DISTRIBUTION OF PATIENTS IN EACH CLASSIFICATION

GROUP	MALE	FEMALE	TOTAL
Cause unknown	69	55	124
Cause known	63	32	95
Mongoloid	31	28	59
Total	163	115	278

by use of more cells with smaller expectations rather than inflexible use of minimum expectations of five. The expected values were calculated on the basis of data given by Race, Mourant, Lawler and Sanger (1948) and by Race and Sanger (1950).

RESULTS

Table 2 shows the distribution of the ABO blood groups among the patients. A chi-square analysis of the ABO blood group distribution of each of the three groups was performed, with the results shown in table 3. It will be seen by inspecting sub-table A of table 3 that the "cause unknown" population cannot be considered, on the basis of these data, as a part of the general population. The P value obtained from the chi-square analysis shows that the deviation in the ABO blood group frequencies between the "cause unknown" group and the general population is probably not due to chance. (Fisher, 1948.) The high

TABLE 2. DISTRIBUTION OF ABO BLOOD GROUPS AMONG PATIENTS

GROUP	TYPE A	TYPE B	TYPE AB	TYPE O	TOTAL
Cause unknown	36	22	5	61	124
Cause known	39	10	3	43	95
Mongoloid	24	7	4	24	59
Total	99	39	12	128	278

P value obtained for the "cause known" group (sub-table B of table 3) shows that the ABO blood group frequencies of this group conform with those of the general population very closely and further serves to accentuate the divergence of the "cause unknown" group. On the basis of the P value obtained for the mongoloid group in sub-table C of table 3, the difference between it and the general population is probably due to chance.

The distribution of ABO group incompatible pairs found in the three groups examined is shown in table 4. The mother-child pairs were classified on the basis of the incompatible antigen, i.e. A or B, and a chi-square analysis of these data was made with the results shown in table 5. The class "Incompatible Antigen A" includes the following pairs: Mother O—Child A; Mother B—Child A; and Mother B—Child AB. The class "Incompatible Antigen B" includes the following pairs: Mother O—Child B; Mother A—Child B; and Mother A—Child AB. In each group the value of P was determined for two degrees of freedom.

Inspection of the P values obtained in table 5 shows no significant difference between the "cause unknown" group and the general population. The data for the "cause known" group, too, along with those for the mongoloid group fit well those of the general population.

TABLE 3. CHI-SQUARE ANALYSIS OF THE ABO BLOOD GROUP FREQUENCIES

Sub-table A Cause Unknown Group

BLOOD GROUP	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	36	51.7	15.7	4.77
B	22	10.7	11.3	11.93
AB	5	3.7	1.3	0.46
O	61	57.9	3.1	0.17
Total	124	124.0		17.33

$\chi^2 = 17.33$; D.F. = 3; $P < .001$

Sub-table B Cause Known Group

BLOOD GROUP	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	39	39.6	0.6	0.009
B	10	8.2	1.8	0.395
AB	3	2.8	0.2	0.014
O	43	44.4	1.4	0.044
Total	95	95.0		0.462

$\chi^2 = 0.462$; D.F. = 3; P = .93

Sub-table C Mongoloid Group

BLOOD GROUP	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	24	24.6	0.6	0.015
B	7	5.1	1.9	0.708
AB	4	1.8	2.2	2.689
O	24	27.5	3.5	0.445
Total	59	59.0		3.857

$\chi^2 = 3.857$; D.F. = 3; P = .28

TABLE 4. DISTRIBUTION OF ABO GROUP INCOMPATIBLE MOTHER-CHILD PAIRS

GROUP	CAUSE UNKNOWN		CAUSE KNOWN		MONGOLOID	
	No.	(%)	No.	(%)	No.	(%)
Mother O—Child A	13	10.5	10	10.5	5	8.5
Mother O—Child B	5	4.0	5	5.3	1	1.7
Mother A—Child B	4	3.2	1	1.1	0	0.0
Mother A—Child AB	2	1.6	2	2.1	1	1.7
Mother B—Child A	0	0.0	0	0.0	3	5.1
Mother B—Child AB	2	1.6	1	1.1	3	5.1
Total incompatible pairs	26	21.0	19	20.0	13	22.0

TABLE 5. CHI-SQUARE ANALYSIS OF ABO INCOMPATIBLE MOTHER-CHILD PAIR DATA

Sub-table A Cause Unknown Group

INCOMPATIBLE ANTIGEN	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	15	17.6	2.6	0.384
B	11	6.6	4.4	2.933
None	98	99.8	1.8	0.032
Totals	124	124.0		3.349

$\chi^2 = 3.349$; D.F. = 2; P = .19

Sub-table B Cause Known Group

INCOMPATIBLE ANTIGEN	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	11	13.5	2.5	0.463
B	8	5.1	2.9	1.649
None	76	76.4	0.4	0.002
Totals	95	95.0		2.114

$\chi^2 = 2.114$; D.F. = 2; P = .36

Sub-table C Mongoloid Group

INCOMPATIBLE ANTIGEN	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
A	11	8.4	2.6	0.805
B	2	3.2	1.2	0.450
None	46	47.4	1.4	0.041
Totals	59	59.0		1.296

$\chi^2 = 1.296$; D.F. = 2; P = .52

TABLE 6. DISTRIBUTION OF RH ANTIGENS AMONG PATIENTS AND GENERAL POPULATION

ANTIGEN	CAUSE UNKNOWN		CAUSE KNOWN		MONGOLOID		GENERAL POPULATION*
	No.	(%)	No.	(%)	No.	(%)	
D	101	81.5	77	81.1	40	67.8	83.2
C	78	62.9	59	62.1	31	52.5	67.8
E	39	31.5	23	24.2	18	30.5	28.7
c	110	88.7	91	95.8	54	91.5	81.3
e	119	96.0	91	95.8	59	100.0	97.6

* Percentages only, after Race, Mourant, Lawler, and Sanger (1948).

The distribution of the Rh antigens in each of the three groups is shown in table 6. The percentage incidence is also shown in each case as well as percentage frequencies for the antigens in the general population.

The chi-square analysis of the Rh antigen frequency data in table 7 shows

TABLE 7. CHI-SQUARE ANALYSIS OF RH ANTIGEN DISTRIBUTION

Sub-table A Cause Unknown Group

ANTIGEN	RESULT	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$	D.F.	P.
D	+	101	103.2	2.2	0.047		
	−	23	20.8	2.2	0.233		
	Totals	124	124.0		$\chi^2 =$ 0.280	1	.61
C	+	78	84.1	6.1	0.442		
	−	46	39.9	6.1	0.933		
	Totals	124	124.0		$\chi^2 =$ 1.375	1	.25
E	+	39	35.6	3.4	0.325		
	−	85	88.4	3.4	0.131		
	Totals	124	124.0		$\chi^2 =$ 0.456	1	.50
c	+	110	100.8	9.2	0.840		
	−	14	23.2	9.2	3.648		
	Totals	124	124.0		$\chi^2 =$ 4.488	1	.04
e	+	119	121.0	2.0	0.033		
	−	5	3.0	2.0	1.333		
	Totals	124	124.0		$\chi^2 =$ 1.366	1	.25

Sub-table B Cause Known Group

ANTIGEN	RESULT	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$	D.F.	P.
D	+	77	79.0	2.0	0.051		
	−	18	16.0	2.0	0.250		
	Totals	95	95.0		$\chi^2 =$ 0.301	1	.60
C	+	59	64.4	5.4	0.453		
	−	36	30.6	5.4	0.953		
	Totals	95	95.0		$\chi^2 =$ 1.406	1	.24
E	+	23	27.3	4.3	0.677		
	−	72	67.7	4.3	0.273		
	Totals	95	95.0		$\chi^2 =$ 0.950	1	.34
c	+	91	77.2	13.8	2.467		
	−	4	17.8	13.8	10.699		
	Totals	95	95.0		$\chi^2 =$ 13.166	1	<.001
e	+	91	92.7	1.7	0.031		
	−	4	2.3	1.7	1.257		
	Totals	95	95.0		$\chi^2 =$ 1.288	1	.25

TABLE 7. CONTINUED

Sub-table C Mongoloid Group

ANTIGEN	RESULT	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o-e)^2/e$	D.F.	P.
D	+	40	49.1	9.1	1.687		
	−	19	9.9	9.1	8.365		
	Totals	59	59.0		$\chi^2 = 10.052$	1	.003
C	+	31	40.0	9.0	2.025		
	−	28	19.0	9.0	4.263		
	Totals	59	59.0		$\chi^2 = 6.288$	1	.013
E	+	18	16.9	1.1	0.072		
	−	41	42.1	1.1	0.029		
	Totals	59	59.0		$\chi^2 = 0.101$	1	.76
c	+	54	48.0	6.0	0.750		
	−	5	11.0	6.0	3.273		
	Totals	59	59.0		$\chi^2 = 4.023$	1	.05
*e**	+	59	57.6	1.4	0.034		
	−	0	1.4	1.4	1.400		
	Totals	59	59.0		$\chi^2 = 1.434$	1	.24

* Expected value in one class too small to yield valid results.

TABLE 8. DISTRIBUTION OF RH GENOTYPES AMONG PATIENTS AND GENERAL POPULATION

GENOTYPE	CAUSE UNKNOWN		CAUSE KNOWN		MONGOLOID		GENERAL POPULATION*
	No.	(%)	No.	(%)	No.	(%)	
DCe/DCe	13	10.5	4	4.2	5	8.5	17.7
DCe/DcE	17	13.7	10	10.5	8	13.6	11.9
DCe/dce	44	35.5	44	46.3	18	30.5	32.7
DCe/dCe	1	0.8	0	0.0	0	0.0	0.8
DCe/dcE	1	0.8	0	0.0	0	0.0	1.0
DcE/DcE	4	3.2	2	2.1	0	0.0	2.0
DcE/DCE	1	0.8	0	0.0	0	0.0	0.07
DcE/dce	15	12.1	9	9.5	9	15.3	11.0
DcE/dcE	0	0.0	1	1.1	0	0.0	0.3
Dce/dce	6	4.8	6	6.3	0	0.0	2.0
DCE/dce	0	0.0	1	1.1	0	0.0	0.2
dce/dce	20	16.1	18	18.9	18	30.5	15.1
dce/dCe	1	0.8	0	0.0	0	0.0	0.8
dce/dcE	1	0.8	0	0.0	1	1.7	0.9

* Percentages only, after Race, Mourant, Lawler, and Sanger (1948).

TABLE 9. CHI-SQUARE ANALYSIS OF RH GENOTYPE FREQUENCIES OF PATIENTS

Sub-table A Cause Unknown Group

GENOTYPE	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
DCe/DCe	13	21.9	8.9	3.617
DCe/DcE	17	14.8	2.2	0.327
DCe/dce	44	40.5	3.5	0.302
DcE/DcE	4	2.5	1.5	0.900
DcE/dce	15	13.6	1.4	0.144
Dce/dce	6	2.5	3.5	4.900
dce/dce	20	18.7	1.3	0.090
Others*	5	9.5	4.5	2.132
Totals	124	124.0		12.412

$\chi^2 = 12.412$; D.F. = 7; P = .09

* Rare genotypes, including: *DCe/dCe, DCe/dcE, DcE/DCE, dce/dCe, dce/dcE.*

Sub-table B Cause Known Group

GENOTYPE	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
DCe/DCe	4	16.8	12.8	9.752
DCe/DcE	10	11.3	1.3	0.150
DCe/dce	44	31.1	12.9	5.351
DcE/DcE	2	1.9	0.1	0.005
DcE/dce	9	10.5	1.5	0.214
Dce/dce	6	1.9	4.1	8.847
dce/dce	18	14.3	3.7	0.957
Others*	2	7.2	5.2	3.756
Totals	95	95.0		29.032

$\chi^2 = 29.032$; D.F. = 7; P < .001

* Rare genotypes, including: *DcE/dcE, DCE/dce.*

Sub-table C Mongoloid Group

GENOTYPE	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
DCe/DCe	5	10.4	5.4	2.804
DCe/DcE	8	7.0	1.0	0.143
DCe/dce	18	19.3	1.3	0.088
DcE/dce	9	6.5	2.5	0.962
dce/dce	18	8.9	9.1	9.304
Others*	1	6.9	5.9	5.045
Totals	59	59.0		18.346

$\chi^2 = 18.346$; D.F. = 5; P = .004

* Rare genotypes, including: *dce/dcE.*

a general agreement between the groups examined and the general population. Only in the case of the c antigen are there significant differences between the expected and observed values. In all cases the observed value exceeds that expected. The Mongoloid group shows as well, a variation in the D and C antigen distributions. The expected number here, in both cases, exceeds the observed number.

Table 8 shows the distribution of the Rh genotypes in the three groups. The frequency in the general population of each of the genotypes is also given. It will be noted that all of the genotypes are not represented in the table since some of the rarer combinations were not found in this investigation. The combined frequency of these rare genotypes is approximately three per cent.

Table 9 shows the results of the chi-square analysis of the genotype frequency data. In each of the sub-tables the genotypes with very low expected values are grouped together. The rare genotypes which were encountered in each group are indicated below each table. The number of degrees of freedom used in determining the P value for each sub-table varies according to the number of classes observed in each of the three groups examined. While the P value for the "cause unknown" group does not show any significant deviation from the general population, the P values for the "cause known" and for the mongoloid groups do. In the case of the "cause known" group, the low P value is due to an excess of (1) *DCe/dce* individuals; and (2) to a lesser extent of

TABLE 10. DISTRIBUTION OF RH FACTOR INCOMPATIBILITIES

ANTIGEN	COMPATIBILITY	GROUP			
		Cause Unknown	Cause Known	Mongoloid	General Population
D	No. compatible	117	86	56	
	No. incompatible	7	9	3	
	% incompatible	5.65	9.47	5.08	9.92
C	No. compatible	109	80	55	
	No. incompatible	15	15	4	
	% incompatible	12.10	15.79	6.78	13.92
E	No. compatible	112	88	53	
	No. incompatible	12	7	6	
	% incompatible	9.68	7.37	10.17	11.08
c	No. compatible	118	90	57	
	No. incompatible	6	5	2	
	% incompatible	4.84	5.26	3.39	10.62
e	No. compatible	118	95	57	
	No. incompatible	6	0	2	
	% incompatible	4.84	0.00	3.39	2.04

TABLE 11. CHI-SQUARE ANALYSIS OF RH ANTIGEN INCOMPATIBILITY DATA

Sub-table A Cause Unknown Group

ANTIGEN	CONDITION	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$	D.F.	P
D	Inc.	7	12.3	5.3	2.284		
	Com.	117	111.7	5.3	0.251		
	Totals	124	124.0		$\chi^2 = 2.535$	1	.12
C	Inc.	15	17.3	2.3	0.306		
	Com.	109	106.7	2.3	0.050		
	Totals	124	124.0		$\chi^2 = 0.356$	1	.57
E	Inc.	12	13.7	1.7	0.211		
	Com.	112	110.3	1.7	0.026		
	Totals	124	124.0		$\chi^2 = 0.237$	1	.65
c	Inc.	6	13.2	7.2	3.927		
	Com.	118	110.8	7.2	0.468		
	Totals	124	124.0		$\chi^2 = 4.395$	1	.04
e	Inc.	6	2.5	3.5	4.900		
	Com.	118	121.5	3.5	0.101		
	Totals	124	124.0		$\chi^2 = 5.001$	1	.03

Sub-table B Cause Known Group

ANTIGEN	CONDITION	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$	D.F.	P
D	Inc.	9	9.4	0.4	0.017		
	Com.	86	85.6	0.4	0.002		
	Totals	95	95.0		$\chi^2 = 0.019$	1	.89
C	Inc.	15	13.2	1.8	0.245		
	Com.	80	81.8	1.8	0.040		
	Totals	95	95.0		$\chi^2 = 0.285$	1	.61
E	Inc.	7	10.5	3.5	1.167		
	Com.	88	84.5	3.5	0.145		
	Totals	95	95.0		$\chi^2 = 1.312$	1	.25
c	Inc.	5	10.1	5.1	2.575		
	Com.	90	84.9	5.1	0.306		
	Totals	95	95.0		$\chi^2 = 2.881$	1	.09
e[s]	Inc.	0	1.9	1.9	1.900		
	Com.	95	93.1	1.9	0.039		
	Totals	95	95.0		$\chi^2 = 1.939$	1	.17

TABLE 11. CONTINUED

Sub-table C Mongoloid Group

ANTIGEN	CONDITION	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o-e)^2/e$	D.F.	P
D	Inc.	3	5.9	2.9	1.425		
	Com.	56	53.1	2.9	0.158		
	Totals	59	59.0		$\chi^2 = 1.583$	1	.21
C	Inc.	4	8.2	4.2	2.151		
	Com.	55	50.8	4.2	0.347		
	Totals	59	59.0		$\chi^2 = 2.498$	1	.13
E	Inc.	6	6.5	0.5	0.038		
	Com.	53	52.5	0.5	0.005		
	Totals	59	59.0		$\chi^2 = 0.043$	1	.95
c	Inc.	2	6.2	4.2	2.845		
	Com.	57	52.8	4.2	0.334		
	Totals	59	59.0		$\chi^2 = 3.179$	1	.08
*e**	Inc.	2	1.2	0.8	0.533		
	Com.	57	57.8	0.8	0.011		
	Totals	59	59.0		$\chi^2 = 0.544$	1	.47

Inc. = Incompatible Com. = Compatible

* Expected value too small to yield valid results.

Dce/dce persons. Furthermore the observed number of *DCe/DCe* individuals was far below that expected. For the mongoloid group, the deviation from the general population may be attributed, almost entirely, to the large number of *dce/dce* individuals included in the group.

The distribution of Rh factor incompatibilities is given in table 10. The percentage incidence of incompatibility expected in the general population has been computed and included in the table. The computations were based on the gene frequencies for a population assumed to be mating at random. A chi-square analysis of these data was performed, and appears in table 11. The expected values in each case are based on the frequency of incompatibility in the general population. Inspection of table 11 will reveal that the expected values for e antigen incompatibility in the "cause known" and mongoloid groups are too small to yield valid results. (The computations are here included for the sake of uniformity.) In general, the P values do not reveal any significant differences between the selected groups studied and the general population. However, in the case of the "cause unknown" group, there were fewer c antigen incompati-

TABLE 12. FREQUENCIES OF MULTIPLE RH FACTOR INCOMPATIBILITIES

INCOMPATIBLE FACTORS	GROUP	NUMBER	PERCENTAGE
DC	Cause unknown	1	0.8
	Cause known	6	6.3
	Mongoloid	2	3.4
	General population		6.8
DE	Cause unknown	0	0.0
	Cause known	2	2.1
	Mongoloid	1	1.7
	General population		2.3
DCE	Cause unknown	0	0.0
	Cause known	1	1.1
	Mongoloid	0	0.0
	General population		0.036
CE	Cause unknown	0	0.0
	Cause known	1	1.1
	Mongoloid	0	0.0
	General population		0.041
Ce	Cause unknown	1	0.8
	Cause known	0	0.0
	Mongoloid	2	3.4
	General population		1.007
cE	Cause unknown	3	2.4
	Cause known	2	2.1
	Mongoloid	0	0.0
	General population		2.8

bilities than expected, and more e antigen incompatibilities which serve to lower the P value beyond the limit of significance.

In addition to single Rh factor incompatibilities, each family studied was examined for multiple incompatibilities. The results of this examination are shown in table 12. Only incompatibilities which were found in this investigation are included in the table. In each, the expected percentage incidence in the general population of the incompatibility is included. No chi-square analysis was made for these data since the class size in each group was too small to yield valid results and pooling of classes would lower the power of the test to an unmeaningful level.

The frequencies of combined ABO and Rh factor incompatibilities were determined for each of the three groups under investigation, and appear in table 13. Table 14 shows the results of a chi-square analysis of the combined ABO and Rh factor incompatibilities for each of the three groups. In each of the sub-tables the multiple incompatible groups have been pooled together for

TABLE 13. FREQUENCY OF MOTHER-CHILD PAIRS SHOWING MULTIPLE RH AND ABO GROUP INCOMPATIBILITIES

Sub-table A Cause Unknown Group

ABO GROUPS		RH GROUPS	NO.	%	% IN GENERAL POPULATION
Mother	Child				
O	A	*D*	1	0.81	1.19
O	B	*C*	1	0.81	0.39
O	B	*E*	1	0.81	0.31
A	B	*C*	1	0.81	0.15
A	B	*c*	1	0.81	0.11
B	AB	*Ce*	1	0.81	0.01

Sub-table B Cause Known Group

ABO GROUPS		RH GROUPS	NO.	%	% IN GENERAL POPULATION
Mother	Child				
O	A	*D*	1	1.05	1.19
O	A	*C*	2	2.11	1.67
O	A	*DC*	1	1.05	0.81
O	B	*c*	1	1.05	0.30

Sub-table C Mongoloid Group

ABO GROUPS		RH GROUPS	NO.	%	% IN GENERAL POPULATION
Mother	Child				
B	A	*E*	1	1.69	0.12
B	A	*c*	1	1.69	0.11
B	AB	*E*	2	3.39	0.13

statistical purposes. The P values obtained show no significant deviation of any of the selected groups from the general population.

DISCUSSION

It appears from the data presented here that no clear relationship between blood group incompatibility and mental deficiency exists. The general agreement between the data for the "cause known" group which served as a control, and those for the general population indicates that the size of the sample is adequate.

In general, the results here agree with those of Zwerling, Gold, Jervis, and Ginsberg (1951). The samples were subjected to more tests in this investigation than in the one by Zwerling et al., but the overall results are very similar. Böök, Grubb, Engleson, and Larson reported a similar investigation in 1949. While their study involved only one of the Rh factors, the D factor, the results here agree with those obtained in their investigation.

TABLE 14. CHI-SQUARE ANALYSIS OF MULTIPLE RH AND ABO GROUP INCOMPATIBILITY DATA

Sub-table A Cause Unknown Group

CLASS	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
Multiple incompatiblity	6	11.5	5.5	2.630
None	118	112.5	5.5	0.269
Totals	124	124.0		2.899

$\chi^2 = 2.899$; D.F. = 1; P = .09

Sub-table B Cause Known Group

CLASS	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
Multiple incompatibility	5	8.8	3.8	1.641
None	90	86.2	3.8	0.168
Totals	95	95.0		1.809

$\chi^2 = 1.809$; D.F. = 1; P = .18

Sub-table C Mongoloid Group

CLASS	OBSERVED	EXPECTED	$\lvert o - e \rvert$	$(o - e)^2/e$
Multiple incompatibility	4	5.5	1.5	0.409
None	55	53.5	1.5	0.042
Totals	59	59.0		0.451

$\chi^2 = 0.451$; D.F. = 1; P = .50

The distribution of the ABO blood types in the "cause unknown" group is quite different from that expected. An excessive number of Type B individuals was found, whereas the number of Type A patients was considerably below that expected. This suggests that perhaps the ABO types are somehow involved in the etiology of mental deficiency. However, when the mother-child pairs in this group are examined for frequency of incompatibility, the statistical analyses show a good fit of these data with those expected in the general population. This refutes the hypothesis that immunization of the mother to the A or B antigens may have a role in causing mental deficiency. Furthermore, this atypical distribution of the ABO blood types of the experimental group was not found by any of the previous investigators. It would seem therefore, that this distribution is due to chance.

The distribution of the Rh antigens, genotypes, and incompatible mother-child pairs among the groups studied conforms generally with that of the general population. In nearly all cases, the statistical analysis indicates that the selected population of mentally deficient individuals may be considered as a part of the general population. Among the exceptional cases which did not

conform with the data for the general population, many are due to genotypes of very low frequency. The order of magnitude of these is such that in a sample ten times the size of the present one, no additional examples of these genotypes would be expected. However, in some cases, frequencies of genotypes of common occurrence were found to be quite different from the expected values. The *DCe/DCe* genotype frequency was below that expected in all three groups. In the mongoloid group, the *dce/dce* genotype was found approximately twice as often as expected. For the "cause known" group there were excesses in both the *DCe/dce* and *Dce/dce* groups.

These deviations from the expected frequencies of the general population would, in themselves, give rise to some speculation regarding the role of the Rh factors in the etiology of mental deficiency. However, when the mother-child pairs are examined for incompatibility, the only statistically significant difference from the general population occurs for the c and e antigens in the "cause unknown" group. The number of c incompatible pairs observed is less than half that expected. This would seem to eliminate *c* antigen incompatibility as a possible etiological agent. The number of *e* incompatible pairs observed, however, is over twice the expected value. By observing the values in sub-table A of table 11, it will be seen that by lowering the observed number of *e* incompatible pairs by one, the value of χ^2 becomes 2.551, with P = .12 for one degree of freedom. This value of P is above the .05 significance level. The statistically significant difference between the "cause unknown" group and the general population would seem therefore to be due to one extra mother-child incompatible pair. This being the case, *e* antigen incompatibility may also be eliminated as a causative agent.

When the mother-child pairs are examined for multiple factor incompatibilities (i.e., each pair is incompatible for more than one antigen of the Rh series and/or the ABO series) as suggested by Cotterman (1951, 1952), no clear pattern is apparent. Limiting the examination to antigens in the Rh series, only six types of multiple factor incompatibilities were found. These included four which although rare, are not uncommon in the general population, i.e., their expected frequencies vary from one to seven cases per hundred. However, the remaining two types are very rare; their expected frequencies in the general population being approximately four cases in ten thousand. Inspection of these data shows that both of these extremely rare incompatibility types are due to the same mother-child pair. The CE incompatible type (see table 12) and the DCE incompatible type which were found are of an overlapping nature. The class size of these data is too small to yield any valid statistical results. It appears, therefore, that no positive inference may be drawn regarding multiple Rh factor incompatibility as an agent in the etiology of mental deficiency.

Further examination of the sample populations for ABO group incompatibilities accompanying Rh factor incompatibilities, yielded generally the same

pattern as had previously been obtained. The data obtained for all three groups are not significantly different from the general population. Thus it appears that the selected populations studied in this investigation do not differ from the general population with respect to multiple factor incompatibilities.

An overall evaluation of all the data obtained in this investigation would be in agreement, essentially, with the work of Zwerling et al. (1951), Böök et al. (1949), Cappell (1947), and Gilmour (1950). Although the last three of these studies were concerned only with the D antigen of the Rh series, no further relationships were discovered by investigating the remaining antigens. Zwerling et al. (1951) investigated some of these, but also found no evidence to justify the conclusion that certain of the Rh antigens, besides the D antigen, are involved in the etiology of mental deficiency. Yannett and Lieberman (1944), and Snyder et al. (1945a, 1945b) reported a higher incidence of D factor incompatibility in a selected population of mentally deficient individuals and their mothers than was expected in the general population. The results of this investigation do not confirm their findings.

SUMMARY

Blood samples from 278 mentally deficient patients at three Michigan state institutions were examined for the ABO and Rh antigens. Samples from the mothers of these patients were also obtained and typed. The patients were divided into three groups, based on the etiology of their condition; namely, "cause known," "cause unknown," and mongoloid.

Statistical analyses of the antigen frequency data, the genotype frequency data, and the incidence of simple and multiple mother-child antigen incompatibilities were made using the chi-square test for goodness of fit. Each of the three groups studied was compared with the general population to determine whether they may be considered as discreet populations or as a part of the general population. These statistical analyses show a high degree of conformity of the groups studied with the general population. In each case, where the antigen frequency data or the genotype frequency data indicate a difference between the groups studied and the general population, the analysis of the mother-child incompatibility data shows that this difference is not sufficient to permit relating the mental deficiency to the atypical antigen or genotype frequency. The mother-child simple and multiple incompatibility data for all three groups examined fit closely those expected in the general population.

These results suggest that mother-child incompatibility with regard to any of the antigens examined in this investigation does not play a significant role in the etiology of mental deficiency. Multiple incompatibilities, i.e., mother-child pairs incompatible for more than one antigen of the Rh series and/or the ABO series, were also shown not to be statistically significant as causative agents. While this does not preclude the possibility that maternal isoimmuniza-

tion with any of the Rh factors may be responsible for some cases of mental deficiency, the evidence gathered in this study indicates that no general pattern of isoimmunization may be inferred. It should be stated that the results of this and previous investigations do not exclude further research in this area. While statistically significant samples have been examined, the number of cases investigated is a very small fraction of the total number of individuals afflicted with mental deficiency of unknown etiology. It would seem, therefore, that further research in this area on new samples of mentally deficient patients and their mothers is desirable.

REFERENCES

Böök, J. A., Grubb, R., Engleson, G., and Larson, C. A. 1949. Rh Incompatibility and Mental Deficiency. *Am. J. Hum. Gen.* 1: 66–78.

Cappell, D. F. 1947. The Mother-Child Incompatibility Problem in Relation to the Nervous Sequelae of Hemolytic Disease of the Newborn. *Brain* 70: 486–494.

Cochran, W. G. 1952. The χ^2 Test of Goodness of Fit. *Annals of Math. Stat.* 23: 315–345.

Cotterman, C. W. 1951. Personal Communication.

Cotterman, C. W. 1952. Personal Communication.

Fisher, R. A. 1948. *Statistical Methods for Research Workers*, 10th Rev. Ed. Edinburgh: Oliver and Boyd. pp. 78–113.

Gilmour, D. 1950. The Rh Factor; Its Role in Human Disease, with Particular Reference to Mental Deficiency. *J. Ment. Sci.* 96: 359–392.

Katz, L. 1953. Personal Communication.

Orth, J. 1875. Ueber das Vorkommen von Bilirubinkrystallen bei neugeborenen Kindern. *Virchows Arch.* 63: 447–462.

Race, R. R., Mourant, A. E., Lawler, S. D., and Sanger, R. 1948. The Rh Chromosome Frequencies in England. *Blood* 3: 689–695.

Race, R. R. and Sanger, R. 1950. *Blood Groups in Man.* Oxford: Blackwell. p. 84.

Schmorl, W. 1903. Zur Kenntnis des Ikterus neonatorum insbesondere der dabei auftretenden Gehirnveränderungen. *Verh. Deut. path. Ges.* 6: 109–115.

Snyder, L. H., Schonfeld, M. D., and Offerman, E. M. 1945a. The Rh Factor and Feeblemindedness. *J. Hered.* 36: 9–10.

Snyder, L. H., Schonfeld, M. D., and Offerman, E. M. 1945b. A Further Note on the Rh Factor and Feeblemindedness. *J. Hered.* 36: 334.

Yannett, H. and Liebermann, R. 1944. The Rh Factor in the Etiology of Mental Deficiency. *Am. J. Ment. Defic.* 49: 133–137.

Yannett, H. and Liebermann, R. 1946. Central Nervous System Complications associated with Kernicterus. *J. Am. M. Ass.* 130: 335–340.

Zwerling, I., Gold, H., Jervis, G. A., and Ginsberg, V. 1951. Blood Incomptability Between Mother and Child in Etiology of Mental Deficiency. *Am. J. Dis. Child.* 82: 7–13.

A Case of Syndactylism of the Ring and Little Fingers

ALFRED T. COLLETTE

Department of Plant Sciences, Division of Genetics, Syracuse University, Syracuse, New York

IN A RECENT ISSUE of this Journal, Montagu (1953) reported a pedigree of syndactylism of the middle and ring fingers which provided evidence that some types of syndactylism can be transmitted through the female and male lines and that the condition was due to a dominant gene on the X-chromosome having varying penetrance and expressivity.

FIG. 1. A view of the hands of the propositus showing syndactylism of the ring and little fingers on both hands.

A pedigree of complete syndactylism of the ring and little fingers on both hands was recently brought to the attention of the author which provides additional data on the subject. The propositus (II-5) of the pedigree was a man seventy-eight years old who exhibited complete syndactylism of the ring and little fingers on both hands. There was no record of syndactyly on his side of the family. The ring finger on the right hand was partially and permanently flexed in the direction of flexure—the flexion being between the first and second phalanges. In addition, extension of the first joint of the ring finger was observed on this hand. There was no apparent flexion of the little finger. The flexion of the ring finger of the left hand was between the second and third

Received January 15, 1954.

FIG. 2. A palmar view of the hands of male IV-8 showing the separation of the fingers after two operations.

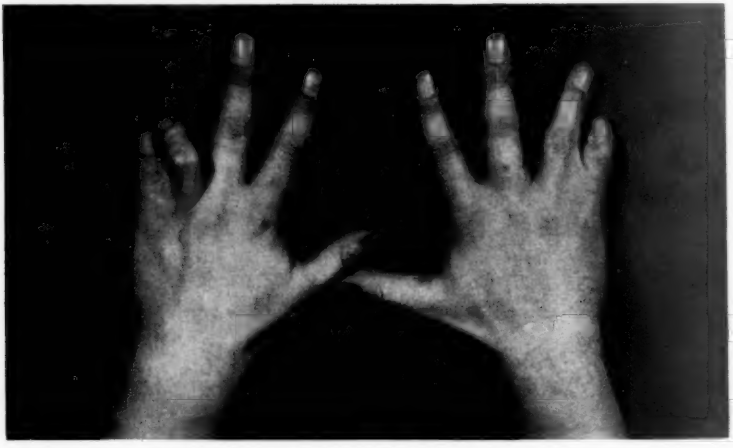

FIG. 3. A dorsal view of the hands of male IV-8

phalanges. There was some extension on this hand but was not as great as exhibited on the right hand. The little finger of the left hand showed no apparent flexion. Some abduction of the fused fingers of both hands was observed but to a greater degree on the left. The nails of the affected fingers on both hands were fused throughout their medial length except near the beds indicating that they were of separate origin. (See fig. 1).

The propositus married twice. By his first marriage he had two daughters and a son. One daughter (III-3) and the son (III-5) displayed the condition.

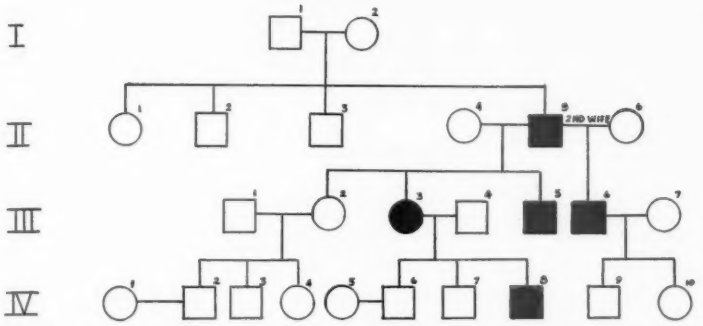

FIG. 4. A pedigree of complete syndactylism of the ring and little fingers on both hands

The son died of pneumonia at the age of two months. The daughter married and had three sons, one of whom was syndactylous. By a second marriage, the propositus had one son (III-6) who displayed the character. This son married but neither his son nor his daughter showed the condition. All the individuals in the pedigree who were syndactylous showed the condition on both hands and with the same degree of expression.

A number of attempts have been made to separate the fingers in two of the males in the pedigree. After six operations, the fingers of one of the males (III-6) were completely separated. The male in generation IV, No. 8 has had two operations to separate the fingers—one at the age of eight and the other at the age of eighteen. The fingers are almost completely separated but independent finger movement is still difficult. (See figs. 2 and 3).

The pedigree (fig. 4) indicates that the inheritance of syndactyly of the ring and little fingers in this particular family is probably due to an autosomal dominant gene and that the condition arose as a mutation in the propositus (II-5).

SUMMARY

A pedigree of syndactylism of the ring and little fingers on both hands is presented. The inheritance of syndactylism of the ring and little fingers in this family is probably due to a dominant autosomal gene and the condition arose as a mutation in the propositus.

ACKNOWLEDGMENTS

I wish to thank Mr. J. F. for his cooperation and his grandfather for supplying me with photographs.

REFERENCES

GATES, R. R. 1946 *Human Genetics*. Chapter XI, Vol. 1, New York: MacMillan Co.

MONTAGU, M. F. ASHLEY, 1953 A pedigree of Syndactylism of the Middle and Ring Fingers, *Am. J. Human Genet.* 5: 70–72.

Fistula Labii Inferioris Congenita and Its Association with Cleft Lip and Palate

ANNE VAN DER WOUDE

Institute of Human Biology, University of Michigan, Ann Arbor, Michigan

FISTULA LABII INFERIORIS CONGENITA was first described by Demarquay in 1845. Descriptions of the fistulae in his and other early reports varied from small pits on the vermilion border of the lip to large snout-like structures in the midline. Pits on the upper lip and its frenum have been reported but those of the lower lip are the more common. These structures have been referred to under such names as accessory salivary glands, supernumerary labial cysts, labial fistulae, mucous glands or cysts, mucoceles, and dermoid cysts. Ludy and Shirazy (1938) have published an extensive review of the literature.

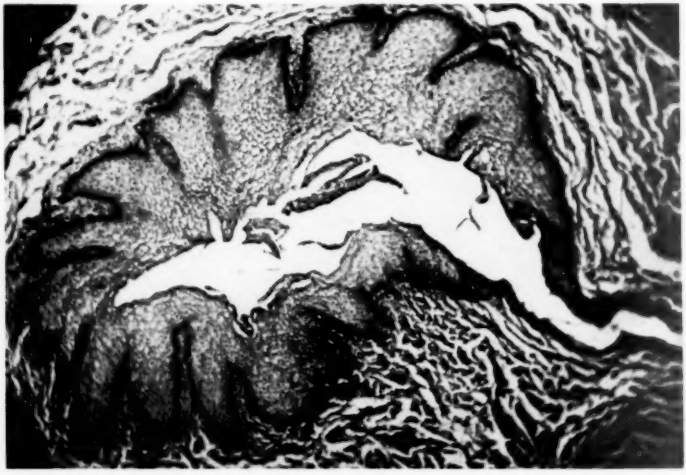

FIG. 1. Transverse section through a fistula labii inferioris

Congenital fistulae usually consist of mucous glands embedded in the submucosa of the lip with the mouths of the communicating ducts lying in a depression or furrow on either side of the midline of the lower lip. The size of the lower lip often depends upon the amount of, and the condition of, the glandular tissue present. There may be more than one set of fistulae. Microscopical examination of a fistula reveals a mucosal tract lined with stratified

Received August 3, 1953.

squamous epithelium which is continuous with the epithelium of the lip (fig. 1). At the base of the tract may be found the acini of several mucous glands with small communicating ducts. The ducts may be open or closed. If open, they may exude a mucin-like fluid. Surgical removal is often carried out if they cause chronic discomfort or if the deformity to the vermilion border of the lip is objectionable. Although various theories have been advanced, the etiology of this peculiar anomaly is as yet unknown.

FAMILIAL OCCURRENCE AND ASSOCIATION WITH CLEFT LIP AND PALATE

To date, about 14 reports of a familial occurrence of this anomaly have appeared in the literature. In approximately 80% of the cases congenital fistulae occur in association with clefts of the lip and palate, a finding which suggests that the two defects may be part of a syndrome. A dominant type of inheritance is apparent for about 75% of the cases.

The first report of labial fistulae to be made in this country was that of De Nancrede in 1912. Two of his cases were a brother and sister who had surgical repair of both cleft lip and cleft palate at the University of Michigan Hospital. Years later, Test and Falls (1947), independently reported on this anomaly in five generations of this same family. In Europe, Murray (1860) described four cases of fistulae of the lower lip in a family in which clefts of the lip and palate were also present. In this family the paternal grandmother had a narrow and high arched palate, the father had bilateral cleft lip and congenital fistulae of the lower lip, but the mother was free of these defects. Of their eight children, two had cleft lip and fistulae of the lower lip, one had fistulae alone, another had a very narrow high arched palate like the grandmother, and four had none of these anomalies.

Shearer (1918), Davis (1935), and Gurney (1940) have described several families in this country with the anomaly. Shearer (1918) reported a case in which the father had congenital fistulae and his child had cleft lip, cleft palate, and fistulae of the lower lip. Davis (1935) reported fourteen cases of congenital fistulae of the lower lip among one thousand cases of congenital deformities of the face. The fourteen cases occurred in three family groups. In three instances fistulae alone were present, but in each case there was a family history of cleft lip and palate through three or four generations. Gurney (1940) reported four cases of fistulae in one family. The mother and one of her sons had labial fistulae as well as both cleft lip and cleft palate. Another son had congenital fistulae only, while yet another son, who died in infancy, was said to have had cleft lip, cleft palate, and fistulae of the lower lip. None of the mother's nine siblings was affected.

Fogh-Andersen (1943) reported eleven cases of labial fistulae in three family groups in Denmark. In one family, the maternal grandmother of the propositus and his mother's maternal aunt had fistulae of the lower lip. The grand-

mother had seven children, three of whom, including the mother of the propositus, had fistulae alone, one had cleft palate and fistulae, another had cleft lip, cleft palate and labial fistulae, and two had no visible defects of the face. The propositus had both clefts of the lip and palate and fistulae of the lower lip. His two brothers were free of anomalies of the face. In another Danish family, the mother had a fistula on the right side of the lower lip and one of her two daughters had a cleft lip. In yet another family, the father had fistulae and both of his daughters had cleft palate and fistulae of the lower lip.

In two accounts showing dominant heredity, there were no associated anomalies of the face. Mason et al. (1940) described a family in which the patient, his father, his paternal uncle and two cousins all had fistulae of the lower lip. Ludy and Shirazy (1938) reported on a family in which the father, three of his five sons, and an only daughter had labial fistulae. The father's maternal aunt and four of her six children also had fistulae of the lower lip.

During the past ten years, two reports of congenital fistulae of the lower lip closely associated with the cheilognathouranoschisis complex involving families from the southeastern part of the State of Michigan have appeared in the literature. In a family described by Straith and Patton (1943), the father and three of his eight children and one grandchild had bilateral cleft lip, cleft palate, and fistulae of the lower lip while one child had bilateral cleft lip and labial fistulae. In the other family, Test and Falls (1947) traced the defect through five generations. The great-great-grandfather had congenital fistulae only and one of his four children, a daughter, had cleft lip and cleft palate. This affected daughter had three children, one of whom, a daughter, had cleft palate and fistulae of the lower lip. This affected daughter, in turn, had two daughters and one son with cleft lip, cleft palate, and labial fistulae, one daughter with cleft palate and fistulae, and two sons with no visible defects. One of the daughters displaying the full triad had seven children among whom only one son had the full triad and one daughter had the fistulae. The other daughter affected with the full triad had one son with cleft palate and one daughter with a cleft of the uvula and fistulae of the lower lip.

The present report will be concerned with five kindreds in which congenital fistulae of the lip occur in association with cleft lip and cleft palate. Two of these kindreds have been described by Straith and Patton in 1943 and by Test and Falls in 1947 and will be brought up to date; the other three kindreds are previously unreported. The proposita in each kindred was a resident of the State of Michigan. The proposita and/or one or more members of her family have received treatment at the University of Michigan Hospital. Attempts at finding a common ancestor for any two of these families have been unsuccessful.

PEDIGREES

Kindred 1903 (Fig. 2)

The proposita for this kindred (IV-7), a 28 year old female normal except for the congenital absence of one lower incisor tooth, consulted the Heredity Clinic regarding her chances of having a child with a cleft lip or palate because of the high incidence of these defects in her family. The family history obtained at the time of her visit was supplemented by an extensive correspondence and several field trips, and is summarized in Fig. 2. All individuals not specifically mentioned were reported as normal.

I-1. ♂, reported by III-4 to have congenital fistulae of the lower lip.

II-1. ♀, reported by several of her children to have had fistulae of the lower lip.

III-1. ♂, reported by his brothers and sisters to have had fistulae of the lower lip. He died at age 50.

III-2. ♀, age 68, reported by several of her brothers and a sister to have fistulae of the lower lip.

III-3. ♂, age 63, reported by III-4 to have fistulae of the lower lip.

III-4. Examination of this man, age 56, showed rather prominent fistulae of the lower lip. He related that they became inflamed at times and occasionally secrete a clear fluid.

III-5. ♂, age 54, reported by his brothers and sisters to have congenital absence of several incisor teeth.

III-6. Examination of this man, age 51, showed prominent bilateral fistulae of the lower lip. The mucous glands frequently become inflamed and surgical removal was being considered.

III-7. ♀, age 46, reported by III-4 to have a cleft lip. Medical records show that surgical repair was carried out at the age of 4 years in the State of New York.

III-8. ♀, age 44, stated that she has fistulae on the lower lip. They have never secreted a fluid and have never caused the slightest discomfort.

IV-1. ♀, age 46, reported by several members of the family to have fistulae of the lower lip.

IV-2. ♂, accidentally killed at an early age, was reported by the family to have had a cleft lip, cleft palate, and fistulae on the lower lip. No record of surgical repair could be obtained.

IV-3. ♀, age 29, had a cleft lip which was repaired at the age of six weeks in a Pennsylvania hospital. She also had fistulae of the lower lip.

IV-4. ♂, age 46, had a cleft palate. Surgical repair was carried out in three stages in a Pennsylvania hospital. Dentition is normal except for small and extremely pointed superior cuspids.

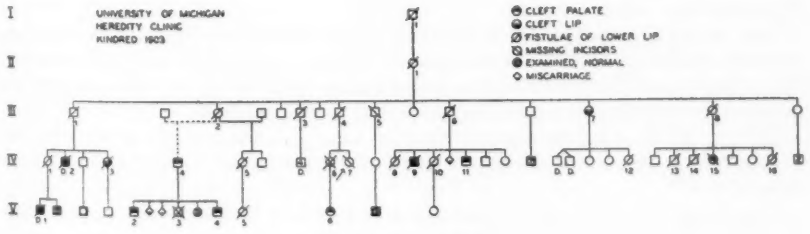

FIG. 2. Kindred 1903

IV-5. ♀, age 40, was reported by one of her aunts to have fistulae of the lower lip.

IV-6. Examination of this woman, age 26, revealed prominent bilateral fistulae on an enlarged lower lip and congenital absence of two upper and two lower incisor teeth. The superior and inferior incisors are large and the superior cuspids are extremely pointed. The third molars failed to erupt.

IV-7. The proposita, age 28, showed the congenital absence of one inferior incisor tooth. She has no other defects of the mouth.

IV-8. ♀, age 24, had prominent fistulae of the lower lip which were recently excised because of their unsightly appearance and discomfort.

IV-9. ♂, age 23, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on February 9, 1931, at the age of six weeks, at which time diagnoses of unilateral cleft of the lip on the right side, cleft palate, and fistulae (accessory mucous glands) on the lower lip were made. Palatorrhaphy was performed on February 14, 1931, and cheilorrhaphy was performed on March 18, 1931. He made three return visits for palatoplasty in 1932, 1933, 1935, and the mucous glands were excised in 1933. There was moderate cosmetic improvement. The patient returned on June 22, 1939, and was advised to consult the Dental School regarding orthodontic treatment for retro-occlusion. Extensive orthodontic treatment, including shortening of the mandible, was performed in a Detroit hospital.

IV-10. ♀, age 22, has fistulae of the lower lip. She was said to have no other anomalies of the face.

IV-11. ♂, age 19, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on August 31, 1936, at the age of 32 months at which time a diagnosis of cleft of the palate extending from the posterior part of the hard palate through the uvula was made. Palatorrhaphy was performed in one stage on September 10, 1936, with excellent results.

IV-12. ♀, age 17, was reported by her cousins, whom she visited three years ago, to have prominent fistulae on the lower lip.

IV-13. ♂, age 24, was reported by his mother and by his cousins to have fistulae of the lip.

IV-14. ♂, age 19, was reported by his mother and by his cousins to have fistulae of the lip.

IV-15. ♀, age 16, was diagnosed as having a cleft of the palate extending up to the alveolar ridge on the right side. Palatorrhaphy was performed at the age of three years in a Pennsylvania hospital. Two permanent superior incisors failed to erupt according to the information obtained from her mother.

IV-16. ♀, age 6, was reported by her mother to have fistulae of the lower lip. She has no other deformities of the face.

V-1. ♂, reportedly died of pneumonia at the age of 2 years shortly after surgical repair for a cleft lip and palate. It was also reported that he had fistulae of the lower lip. Where the repair was done was not known.

V-2. ♂, age 19, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on December 9, 1935, at the age of 23 months. A diagnosis of cleft of the hard and soft palate was made. Palatorrhaphy was performed on December 11, 1935. Palatoplasty for a perforation in the hard palate was performed in 1936 and 1937.

V-3. ♂, age 10, was examined and found to have prominent fistulae of the lower lip. They neither secrete a fluid nor cause discomfort. He also lacks two superior incisor teeth (Fig. 3).

V-4. ♂, age 6, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on September 8, 1947, at the age of 18 months. A diagnosis of incomplete cleft of

FIG. 3. IV-2 of Kindred 1903, a 10-year-old male exhibiting fistulae on an enlarged lower lip and lacking two superior incisor teeth.

the palate extending through the posterior third of the hard palate to the soft palate was made. All deciduous teeth have erupted and are normal in position.

V-5. ♀, reported by an aunt to have had fistulae of the lower lip excised.

V-6. ♀, age 3, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on August 25, 1950, at the age of 10 months at which time a diagnosis of incomplete cleft of the palate extending the length of the soft palate through the middle third of the hard palate was made. Palatorrhaphy was performed on April 3, 1951.

Kindred 343 (Fig. 4)

The proposita was a two-month old female (III-3) with cleft lip and fistulae of the lower lip. Her older brother and sister had had surgical repair for clefts of the lip and palate at the University of Michigan Hospital. The parents of these children are not known to exhibit any defects of the lip or palate.

II-1. ♂, age 39, was reported by his sister (mother of the proposita) to have clefts of the lip and palate, and fistulae of the lower lip.

II-2. ♀, age 37, was reported by her sister to have a cleft of the palate.

III-1. ♂, age 14, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on April 11, 1939, at the age of two months at which time a diagnosis of cleft of the lip on the left side was made. At the time of cheilorrhaphy it was noted that the peculiar configuration of the vermilion tissue of the lower lip was due to the presence of large secreting mucous glands. The child was returned a year later for cheiloplasty and for the removal of the mucous glands in the lower lip, but the parents refused to give permission for further surgery.

III-2. ♀, age 13, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on August 6, 1940, at the age of three weeks. Diagnoses of a cleft of the lip on the right side, and complete cleft of the palate was made. Cheilorrhaphy was performed on August 9, 1940. Palatorrhaphy was performed in two stages in 1942 and 1943.

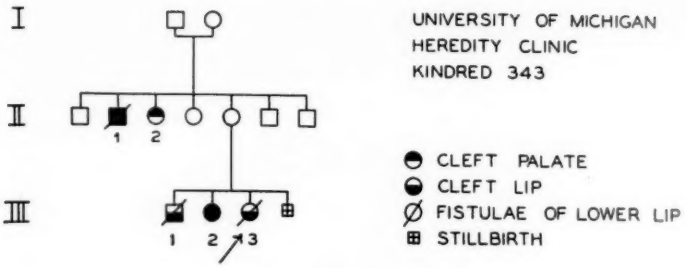

FIG. 4. Kindred 343

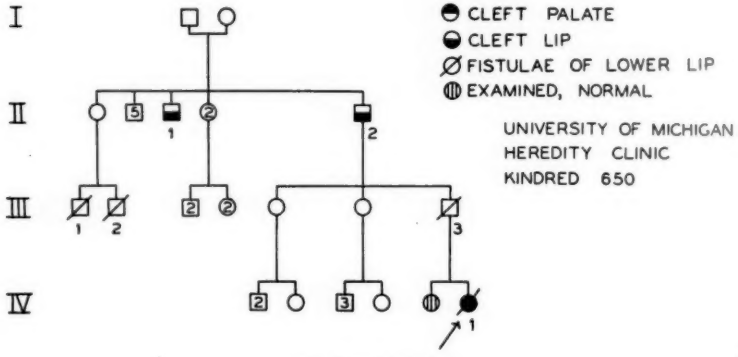

FIG. 5. Kindred 650

III-3. ♀, age 10, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on January 26, 1943, at the age of two months. Diagnoses of complete unilateral cleft of the lip on the right side and fistulae on the lower lip were made. Two fistulae were seen on the right side of the midline and one on the left. Cheilorrhaphy was performed on February 17, 1943, and the mucous glands were excised on March 2, 1943.

Kindred 650 (Fig. 5)

The proposita (IV-1) was referred to us by Dr. C. L. Straith of the Straith Clinic, Detroit, Michigan, to whom we are indebted for the opportunity of studying the family.

II-1, 2. ♂♂, reported by the mother of the proposita to have had clefts of the lip.

III-1, 2. ♂♂, reported by the mother of the proposita to have fistulae of the lower lip.

III-3. ♂, age 56, has fistulae of the lower lip. Examination revealed none of the usual expressions of cleft lip or palate. The ducts of the mucous glands are completely closed over.

IV-1. ♀, age 9, the proposita, was seen in the Straith Clinic where diagnoses of cleft lip on the right side, cleft palate, and fistulae of the lower lip were made.

Kindred 1912 (Fig. 6)

The proposita was a 39 year old woman (III-1) who was contacted in an effort to bring the kindred up to date following the initial report by Straith and Patton in 1943. Verification

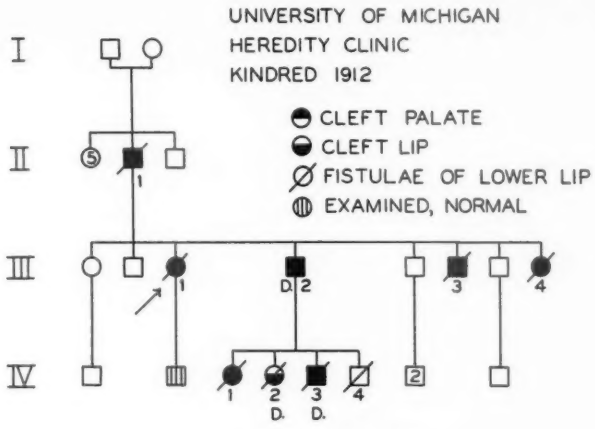

FIG. 6. Kindred 1912

of the diagnoses on the affected members of generation IV were obtained from Dr. C. L. Straith.

II-1. ♂, age 70, had bilateral clefts of the lip and palate. He also has the fistulae of the lower lip.

III-1. The proposita was seen in the Oral Surgery Clinic of the University of Michigan Hospital on May 19, 1930, at age 16 years. Diagnoses of repaired bilateral cleft lip, perforation of the palate, and fistulae on the lower lip were made. Cheiloplasty and approximation of the palate were performed on May 21, 1930. The fistulous mucous glands were excised on December 10, 1930, and a year later a cyst was removed from the lower lip where one of the mucous glands had been previously. Palatoplasty was performed a year later and the cosmetic improvement was quite satisfactory.

III-2. ♂, died at the age of 36, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on July 21, 1930, at the age of 14. Diagnoses of postoperative bilateral cleft lip, cleft palate, and supernumerary labial glands of the lower lip were made. Cheiloplasty and the excision of the mucous glands were performed on December 13, 1930. A year later cysts were removed from the lower lip where the glands had been previously. The supernumerary mucous glands gave the lower lip an unsightly appearance. The mouth of the duct of each gland was about 3 mm. in diameter and caused a mark depression in the lower lip. The ducts were about 1 mm. in depth and would readily accommodate the beaks of a large hemostat. The glands secreted a watery fluid. This man enjoyed only moderate cosmetic improvement because the premaxillary process had been removed in previous surgery in Canada.

III-3. ♂, age 32, was first seen in the Oral Surgery Clinic of the University of Michigan Hospital on October 6, 1930, at the age of 10. He had had four previous operations for the repair of bilateral cleft lip and cleft palate. The fistulae were present on the lower lip. Cheiloplasty, palatoplasty, and excision of the mucous glands were performed on October 8, 1930. As in the case of his brother, the premaxillary process was completely removed in an earlier operation in Canada and the patient presents a short upper lip.

III-4. ♀, age 29, was first seen in the Oral Surgery Clinic of the University of Michigan

Hospital on July 1, 1924, at the age of two months, at which time diagnoses of bilateral cleft lip, cleft palate, and fistulae of the lower lip were made. Approximation of the premaxillary process was performed on July 2, 1924. Palatorrhaphy was performed on September 21, 1927. Cheiloplasty and palatoplasty were performed in several stages over a nineteen year period. The mucous glands were excised in 1928.

IV-1. ♀, age 10, underwent surgery in the Straith Clinic for repair of bilateral cleft lip, cleft palate, and for excision of the mucous glands in the lower lip.

IV-2. ♀, died in infancy, was seen in the Straith Clinic in September 1947. She had a cleft lip and fistulae of the lower lip.

IV-3. ♂, died at age 6, underwent surgery in the Straith Clinic in 1946, for correction of a cleft of the lip, cleft palate, and for removal of mucous glands in the lower lip.

IV-4. ♂, age 4, had fistulae of the lower lip. The mucous glands were removed in 1949 in the Straith Clinic.

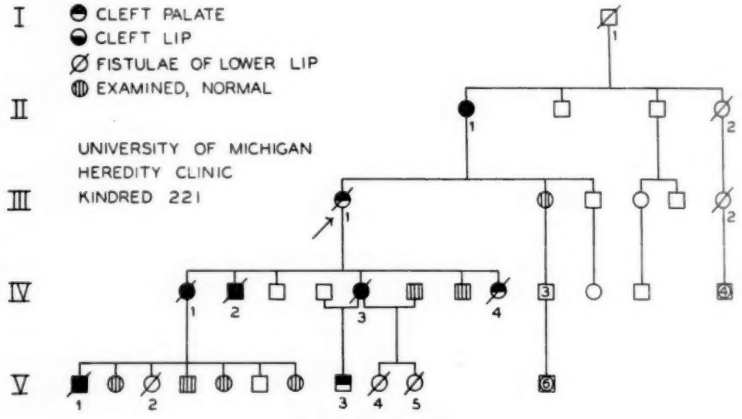

FIG. 7. Kindred 221

Kindred 221 (Fig. 7)

This kindred was described by Test and Falls in 1947. Additional information was obtained from III-1 and her sister.

II-2. This woman was reported by her niece to have had fistulae on the lower lip, but no unusual intonation of the voice was recalled. A photograph from an old family album confirmed the presence of fistulae.

III-2. This woman was also reported to have had fistulae on the lower lip. A photograph confirms this report.

V-5. ♀, age 4, was seen by Dr. H. F. Falls of the Ophthalmology Dept. and reported to have fistulae on the lower lip.

GENETICS

As noted above, the occurrence of fistulae labii inferioris congenita in association with the cheilognathouranoschisis complex has now been described by various investigators in at least fourteen family groups. These

data, together with those of the present paper, are consistent with the hypothesis that the malformation is due to a single dominant gene whose effects may vary from the full triad of cleft lip, cleft palate, and labial fistulae to no detectable departure from normal. There is no evidence of sex linkage, sex limitation, or sex influence.

The variable expressivity of the complex among the affected persons in these kindreds is of special interest. The fistulae may occur alone (25 cases among 94 offspring of affected parents) or they may be associated with cleft lip and/or cleft palate (20 cases among 94 offspring of affected parents). The affected person, no matter how mild the manifestation, is capable of transmitting the anomalies, singly or in combination, to approximately one half of his or her offspring. The degree of dominance and the severity vary from one family group to the next. Kindred 1912 demonstrates direct inheritance with almost complete expression of the full triad through three generations. In contrast, kindred 343 shows a lack of penetrance of the gene in the parent but severe expression in all three of her children. Evidence of mildly affected persons (fistulae only) transmitting the trait with variable degrees of expression is strikingly demonstrated in kindred 1903. Five of the six members in generation III who possess fistulae alone have had offspring expressing a gradient of defects varying from the full triad to fistulae only.

The total number of offspring of affected parents in these five kindreds was 94 (44♂, 50♀) among whom 55 (23♂, 32♀) had malformations of the mouth. Correcting for bias of sampling by subtracting the proposita and the individuals in direct line of ascent from each kindred, the ratio of normal to affected becomes 38:47, essential agreement with a 1:1 ratio. Six males and eight females had either a cleft lip or cleft palate with or without fistulae, eight males and eight females had both cleft lip and cleft palate (all but 2♀ had fistulae also); and nine males and sixteen females had fistulae only. Further details on frequency of occurrence of the various defects in each of the kindreds is given in table 1. It is evident in these kindreds that parents with both cleft lip and cleft palate showed a slight disposition to transmit to their offspring the anomaly in its severest form. Among the severely affected parents, about 28% of their offspring had both cleft lip and cleft palate, 12% had fistulae only, 8% had cleft lip, and 8% had cleft palate. Moreover, cleft lip and/or cleft palate and/or fistulae of the lower lip appear to occur with equal frequency (18.7%) among the offspring of parents affected with either cleft lip or cleft palate. Although several cases of missing incisor teeth are reported in one of the kindreds, there appears to be no direct evidence that a relationship exists between missing incisor teeth in one generation and the occurrence of clefts of the lip and palate in the next.

The frequency of the cheilognathouranoschisis complex in the average population is about 1.5 per thousand. The number of newborn in the State of

TABLE 1. SUMMARY OF THE FREQUENCY OF THE VARIOUS MALFORMATIONS OF THE SYNDROME IN EACH KINDRED

KINDRED	OFFSPRING OF AFFECTED PARENTS						MALFORMATIONS OF THE SYNDROME AMONG AFFECTED OFFSPRING OF AFFECTED PARENTS													
	Normal		Affected		Total		Fistulae cleft lip cleft palate		Fistulae cleft lip		Fistulae cleft palate		Cleft lip cleft palate		Cleft lip		Cleft palate		Fistulae only	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1903	10	10	14	15	24	25	3	—	—	1	—	—	—	—	—	1	4	2	7	11
343	—	—	1	2	1	2	—	—	1	1	—	—	—	1	—	—	—	—	—	—
650	—	3	1	1	1	4	—	1	—	—	—	—	—	—	—	—	—	—	1	—
1912	4	1	4	4	8	5	3	3	—	1	—	—	—	—	—	—	—	—	1	—
221	7	4	3	10	10	14	2	2	—	—	—	2	—	1	—	—	1	—	—	5
	21♂	18♀	23♂	32♀	44♂	50♀	8♂	6♀	1♂	3♀	—	2♀	—	2♀	—	1♀	5♂	2♀	9♂	16♀
Totals.....	39 Normal		55 Affected		94 Offspring		14		4		2		2		1		7		25	

Michigan between 1938 and 1947 was close to one million. We would expect, therefore, about 150 of the babies born each year in Michigan to have cleft lip and/or cleft palate, or a total of 1500 over a ten year period. Eight of the 19 children born in these five kindreds between 1938 and 1947 had cleft lip and/or cleft palate (1♂ and 5♀ had cleft lip and cleft palate, 1♂ had cleft lip, 1♂ had cleft palate). It appears from these figures that we would expect to find cleft lip and/or cleft palate on the same genetic basis as the cases reported in these families in at least 8/1500 or 0.5% of all cleft lip-cleft palate cases. However, in view of the fact that the present communication does not summarize an attempt to locate all persons in the State of Michigan in which this abnormality is present, the actual proportion of cleft lip and cleft palate associated with fistula labii inferioris congenita may be significantly higher.

SUMMARY

Three new pedigrees of fistula labii inferioris congenita associated with cleft lip and palate are reported. Additional information is given on two previously reported pedigrees.

The complex is inherited as if due to a single gene of variable expressivity. Its effects may vary in expression from the full triad of cleft lip, cleft palate, and fistulae of the lower lip to no detectable departure from normal.

The affected person, no matter how mild the manifestation, is capable of transmitting the anomalies, singly or in combination, to approximately one half of his or her offspring. A severely affected parent appears to have more severely affected offspring than does the mildly affected parent. On the other hand, a normal parent with familial history of the defects may have severely affected offspring.

It is estimated that at least 0.5% of all the cases of cleft lip and palate occurring in the State of Michigan in the years 1938 to 1947 have the genetic background described in this paper.

ACKNOWLEDGMENTS

The author is deeply indebted to Dr. James V. Neel for guidance throughout this study.

Appreciation is expressed to Dr. Clare L. Straith of the Straith Clinic, Detroit, for supplying information on several of the kindreds.

REFERENCES

DAVIS, W. B. 1935. Congenital deformities of the face; types found in a series of 1000 cases. *Surg., Gynec., and Obst.* 61: 201–209.

DEMARQUAY, J. N. 1845. Quelques considérations sur le bec-de-lièvre. *Gaz. Méd. de Paris* 13: 52–53.

DE NANCREDE, C. B. 1912. Bilateral congenital fistulae of the lower lip. *Ann. Surgery* 56: 400.

FOGH-ANDERSEN, P. 1943. Fistula labii inferioris congenita. *Saertryk af Tandlaegebladet*, Nr. 9.

GURNEY, C. E. 1940. Congenital pits of lower lip; report of three cases in one family. *West J. Surg.* 48: 753–754.

LUDY, J. B., AND SHIRAZY, E. 1938. Concerning congenital fistulae of the lips; their mooted significance; review of the literature; and report of family with congenital fistulae of the lower lip. *New Internat. Clinics* 3: 75–88.

MASON, M. L., ANSON, B. J., AND BEATON, L. E. 1940. Surgical and anatomical aspects of a case of double lower lip. *Surg., Gynec., and Obst.* 70: 12–17.

MURRAY, J. J. 1860. Undescribed malformation of the lower lip occurring in four members of one family. *Brit. and For. Med.-Chir. Rev.* 26: 502–509.

SHEARER, W. L. 1918. Cleft palate and harelip. *Nat. Dent. Assoc.* 5: 1103–1128.

STRAITH, C. L., AND PATTON, H. S. 1943. Bilateral congenital mucous cysts in three generations. *J.A.M.A.* 123: 693–694 (November 13).

TEST, A. R., AND FALLS, H. F. 1947. Dominant inheritance of cleft lip and palate in five generations. *J. Oral Surg.* 5: 292–297.

An Extension of Two Pedigrees of Hypoglycemosis

R. C. ANDERSON AND IRVINE McQUARRIE

Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota

IN AN EARLIER REPORT (Anderson, R. C. et al., 1950) we described two pedigrees of hypoglycemosis, each with three affected individuals. We suggested that hypoglycemosis probably represents an hereditary metabolic disorder. Since that time five more children have been born into these families, and three of them have developed clinical symptoms and laboratory findings diagnostic of hypoglycemosis. In view of the rarity of this condition, as far as medical reports are concerned, it was deemed important to expand the previously published pedigrees. The corrected pedigrees are shown in figure 1.

New Cases: In Family A, one new case III-6, has appeared. This is a female infant born May 4, 1951. The fasting blood sugar on the second day of life was 22 mg. per cent. On the third day she developed seizures. There was a rapid response initially to ACTH therapy, but later the patient seemed to have developed some refractoriness to the drug. The patient now has strabismus similar to that in each of her brothers. In Family B, two new cases have appeared. One of these, III-13, is a male infant who showed symptoms of hypoglycemia at the age of 12 months. The symptoms were mild, however, and probably would have remained undetected except for the alert observation of the infant's physician-father. Laboratory studies showed a flat glucose tolerance curve with a fasting blood sugar of 24 mg. per cent. This boy has been treated with ACTH with good clinical and laboratory results. The other new case, III-16, is a male infant who developed twitchings of the arms and legs at the age of three months, followed by a definite seizure. The blood sugar level was found to vary from 17 to 33 mg. per cent. The patient responded to ACTH therapy, but later suffered another seizure when therapy was limited to a high-protein, frequent feeding, diet.

The present status of other affected individuals in these two families is as follows:

Family A: III-3 Mentally retarded and continues to have seizures. Blood sugar levels now normal.

III-4 Mentally retarded and continues to have seizures. Blood sugar levels now normal.

III-5 Normal intelligence but poses a behavior problem. Now on high protein diet and blood sugar levels are normal.

Received December 10, 1953.

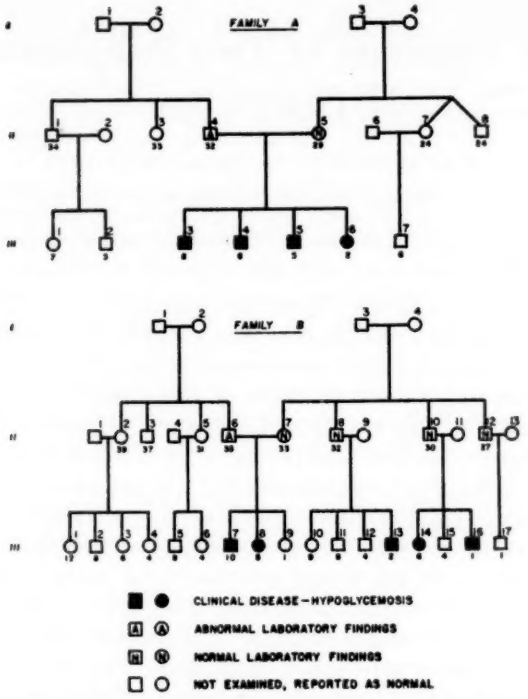

FIG. 1. Present status of two pedigrees of hypoglycemosis

Family B: III-7 Mentally retarded. Blood sugar levels now normal.
III-8 Normal intelligence. Received ACTH therapy for one year. Blood sugar levels now normal.
III-14 Normal intelligence. Blood sugar levels now normal.

One additional family with hypoglycemosis has recently been studied at this hospital. The mother in this case had two single births followed by a set of triplets. Two of the latter developed seizures and were found to have low blood sugar levels and abnormal insulin tolerance curves. Investigation of these triplets showed that two of them were identical individuals, and these two were the ones with hypoglycemosis.

In our earlier report the possibility was raised that affected children might later develop normal blood sugar levels, and that this would interfere with ascertainment of the condition in older individuals. This appears to be borne out by the now-normal blood sugar levels in some of the previously described individuals. This change was probably brought about by both ACTH therapy and spontaneous physiological processes.

The expanded pedigrees do little in further clarifying possible genetic pat-

terns. It is possible that a recessive gene may be involved, especially if hypoglycemosis proves more common than usually believed, or that a dominant gene with variable penetrance and expressivity underlies the condition. Despite the absence of a clear-cut genetic pattern, the occurrence of additional cases in these two families further implicates an hereditary factor.

A more detailed account of these cases and of the subject of hypoglycemosis is currently being prepared by one of the authors (I. M.).

REFERENCE

ANDERSON, R. C., WRIGHT, W. S., BAUER, E. H., AND MCQUARRIE, I. 1950. Familial hypoglycemosis of probable genetic origin. *Am. J. Human Genet.* 2: 264–268.

Evidence for a Hereditary Factor in Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome)[1]

JULIUS D. METRAKOS AND F. CLARKE FRASER

Department of Genetics, McGill University and Department of Medical Genetics, The Children's Memorial Hospital, Montreal

McINTOSH in 1933 described the abnormal findings in a white girl who had "hereditary ectodermal dysplasia, associated with polydactylism and chondrodystrophy." Dwarfism was due to the marked shortening of the legs, the trunk being described as long. The bones of the upper extremities were also reduced in length. The hands and feet were somewhat stubby and a sixth digit was present on the ulnar side of each hand. The teeth, finger and toe nails were rudimentary, but the skin and hair were said to be normal. There was no similar deformity in either the paternal or maternal side of the family; but as Ellis and van Creveld (1940) pointed out later, the parents were first cousins.

It was not until 1940 that Ellis and van Creveld published two additional cases that fitted the description given by McIntosh and thereby concluded that this was a new syndrome. In addition to chondrodystrophy, ectodermal defects and manual polydactyly, both of these patients had cardiac enlargement and a systolic murmur compatible with an interventricular septal defect. The complete syndrome was therefore defined as consisting of a tetrad of abnormalities, namely: a) chondrodysplasia, b) ectodermal dysplasia, c) polydactyly, and d) congenital heart disease.

More recently Weller (1951), Gatto (1951) and Caffey (1952) have reported four more cases and have described in considerable detail the condition now known as the Ellis-van Creveld syndrome. Caffey (1952), in particular, has pointed out that the shortening of the long bones of the extremities is more pronounced in the distal than in the proximal segments.

Only one of the three patients presented by Ellis and van Creveld (1940) had a sibling, and he was normal (table 1, Sibship III). Furthermore none of the varied features of the syndrome was present in any of the near relatives, but the observation that two of the three patients had parents who were first cousins "strongly suggested that the syndrome had been inherited as a recessive gene or genes. . . ." It is the aim of this paper to record the occurrence of

Received March 5, 1954.

[1] Presented in résumé at the annual meeting of the American Society of Human Genetics in Boston (December 28–30, 1953).

TABLE 1. TWELVE CASES OF CHONDROECTODERMAL DYSPLASIA IN TEN SIBSHIPS

SIBSHIP AND CASE	AUTHOR AND YEAR	AGE WHEN LAST REPORTED YEARS/MONTHS	ETHNIC ORIGIN	SIBSHIP	PARENTAL CONSANGUINITY
I-1	McIntosh (1933)	19/0	Jewish	F m	1st cousin
II-2	Ellis and van Creveld (1940)	1/8	English	F*	1st cousin
III-3	Ellis and van Creveld (1940)	4/3	Dutch	M M	No
IV-4	Weller (1951)	2/0	Turkish	U F	No
V-5	Gatto (1951)	15/0	Italian	F *	Yes
VI-6	Caffey (1952)	3/6	—	F F	No
VII-7	"	1/5	—	U U F	No
VIII-8	Present (1954)	14/1	Irish-English	F M M	No
IX-9	"	5/5	French-Canadian	M F F M M F	No
IX-10	"	3/3	French-Canadian		
X-11	"	18/1	English-French	M m F F m F F MM M	No
X-12	"	18/1	English-French		

M = unaffected male F = affected female
M = propositus U = unstated sex
m = miscarriage * = no information on siblings
MM = dizygotic twins.

the syndrome in five additional patients—one "sporadic" case, a brother and sister, and a pair of dizygotic twin boys.

CASE HISTORIES

Dr. J. Scott Dunbar of the Department of Radiology, The Children's Memorial Hospital, and Dr. R. G. Fraser of the Department of Radiology, Royal Victoria Hospital, to whom we are indebted for their invaluable contribution in confirming the diagnosis in the five cases presented below, will publish detailed case histories of these patients emphasizing the radiological findings. In a personal communication they have stated that all of these patients show radiologically the typical shortening of the extremities which is more pronounced in the distal than in the proximal segments. Here, therefore, only the clinical findings will be presented, and will be confined for the most part to the description necessary to show that the cases do represent the Ellis-van Creveld syndrome.

In table 1 are listed, in their order of appearance in the literature, twelve cases of the Ellis-van Creveld syndrome. In order to conform to the table. th five new cases are numbered 8, 9, 10, 11 and 12.

Case 8. (table 1, Sibship VIII, Propositus). L. S. is the 14-year-old son of an Irish-Canadian father, and an English mother both of whom are 47 years old. He was born at full term and there was no significant antenatal history.

This boy has abnormally short upper and lower extremities, the reduction in length being most pronounced distally. His trunk is of average length. Two years ago, bilateral osteotomies of the upper tibiae were performed in order to correct his bilateral genu valgum. A supernumerary digit on the ulnar side of each hand has been removed. An extra digit between the third and fourth toes of each foot still remains. The teeth are hypoplastic and malformed. The nails of the hands and feet are thin and small, but the hair appears normal in quantity and distribution. The sulcus between the upper lip and gum is almost obliterated. There is a systolic murmur near the apex which has been considered as functional by several physicians. A congenital epispadias is present. Apart from his physical deformities this boy has been in relatively good health and there is no indication of impaired intelligence.

The parents, an older sister (16 years) and a younger brother (10 years) are alive and well with no pertinent medical history. No trace of the condition could be found in either the paternal or maternal kindreds, and the parents are not related.

Case 9. (table 1, Sibship IX, Propositus) M. R. is the five-year-old son of French-Canadian parents. The father and mother are 38 and 33 years old respectively. Parturition was one month premature but otherwise normal. There is no significant ante-natal history.

This boy has the characteristic dwarfing and other signs of the Ellis-van Creveld syndrome. There is marked shortening of the extremities, most pronounced distally. The supernumerary finger on the ulnar side of each hand has been removed surgically. There is no polydactyly of the feet. Finger and toe nails are hypoplastic and somewhat irregular in shape. The teeth are also grossly deformed and hypoplastic but the hair appears normal except for a slight thinning of the eyebrows. The mucous membrane of the upper lip attaches to the lower margin of the gum, obliterating the normal sulcus between lip and gum. The heart sounds are normal and there are no murmurs. There is a slight epispadias. The general health is good, and the intelligence appears normal, although no psychometric tests were done.

The parents, three older siblings (10, 8 and 7 years) and a younger brother (5 years) are alive and well and free of the condition; however, a younger sister is the subject of Case 10. The parents are not related.

Case 10. (table 1, Sibship IX, Secondary case). D. R. is the three-year-old sister of the patient described as Case 9. Parturition was at term and uncomplicated. The antenatal history was normal.

This girl has deformities similar to those of her brother. She is dwarfed because of the marked shortening of the legs but her trunk is at least of average

FIG. 1. Case 9 (left) and case 10 (right) with a brother who is intermediate in age (middle).

length. The upper extremities also show the characteristic shortening. She, too, has an extra finger on the ulnar side of each hand, without polydactyly of the feet. The nails of the hands and feet are small and thin. The front teeth have never appeared and the others are carious. The eyebrows are thin but the hair in other parts of the body appears normal. The sulcus between the upper lip and gum is absent. There are no cardiac murmurs. Her general health is good and there is no indication of impaired intelligence.

Cases 9 and 10 are compared in fig. 1 with their normal brother who is intermediate in age.

Case 11. (table 1, Sibship X, Propositus). E. B. is an 18-year-old son of an American father with French-Canadian ancestry and an Anglo-French mother. The father died four years ago when 57 years old of arteriosclerotic heart disease with hypertension. The mother who is now 58 years old, had a hysterectomy in 1946. The birth is described as full-term and uneventful. This patient is the twin brother of Case 12. On the basis of dissimilarities in eye-colour and blood groups (one is Kell positive and the other Kell negative), the twins have been adjudged dizygotic (fig. 2).

This boy has always been healthy and his muscular development is excellent. The characteristic shortness of the legs and bilateral genu valgum account for his dwarfism. There is one extra digit on the ulnar side of each hand. The de-

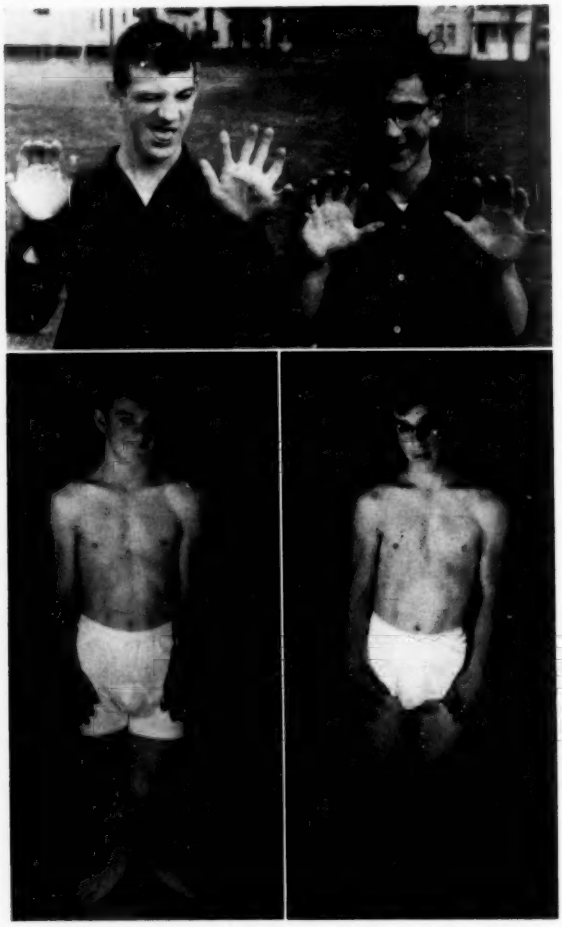

FIG. 2. Case 11 (right) and 12 (left): dizygotic twins concordant for chondroectodermal dystrophy, discordant for microcephaly.

fective nails are now extremely thick and hard. The mother states that up until three or four years ago the nails were thin and short. The teeth are markedly deformed and the sulcus between upper lip and gum is absent (fig. 3). The hair of the pubis is scanty but elsewhere it is normal. The intelligence of this boy is slightly below average (I.Q. = 90 by the Terman test) but within normal limits. The heart sounds are normal and there are no murmurs.

The twins are the product of the eighth pregnancy (table 1, Sibship X). The second and fifth pregnancies terminated as miscarriages at two and three

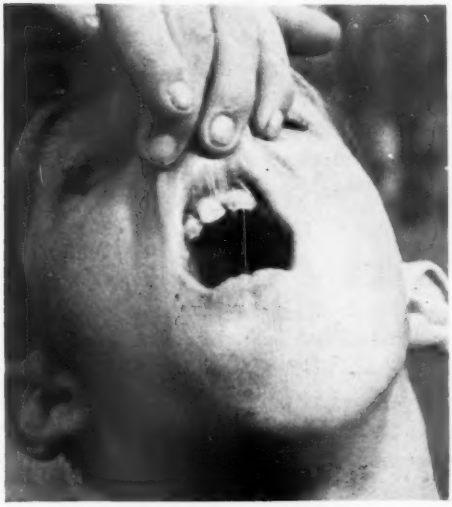

FIG. 3. Case 11, showing absence of sulcus between upper lip and gum, defective teeth and small, thick nails.

months respectively. Five older siblings (35, 32, 31, 28 and 26 years) are in good health and have no congenital defects. The second and third oldest sisters have two normal children each. One younger brother has a complete bilateral cleft lip and palate. There is no parental consanguinity and no history of any defect similar to that of the patient on either side of the family with the exception, of course, of the patient's twin brother.

Case 12. (table 1, Sibship X, Secondary Case) F. B. is the dizygotic twin brother of Case 11 (fig. 2).

This boy, like his twin brother, is very muscular and strong. The trunk is normal in length but the extremities are short. Bilateral genu valgum accentuates the dwarfness. There is manual polydactyly, and the finger and toe nails are similar to those described in his twin brother. The teeth are carious and hypoplastic. The upper and lower sulci between teeth and gum are obliterated. The hair is normal. In addition this boy is a microcephalic imbecile (I.Q. = 49 by the Terman test) with a history of grand mal and petit mal convulsive attacks almost from the time of birth. He has bilateral congenital cataracts. The heart sounds are normal and there are no murmurs or symptoms referable to the cardiovascular system.

SUMMARY OF CASE HISTORIES

The five cases reported above have occurred in three sibships: a sporadic case, two in a brother and sister, and two in dizygotic twin boys. All five pa-

tients have 1) shortening of the limbs, progressive distally; 2) an extra digit on the ulnar side of each hand; 3) ectodermal dysplasia affecting the nails and teeth; and 4) a reduced or obliterated sulcus between the upper lip and gum. In none of the patients was there any clinical evidence of congenital heart disease. There was no history of the condition in the six parents, twelve grand-parents, thirty-seven uncles and aunts, and thirty cousins of the probands. None of the three marriages was consanguineous.

DISCUSSION

A review of the literature has disclosed seven cases which possess at least the three basic features of the Ellis-van Creveld syndrome—chondrodysplasia, ectodermal dysplasia, and manual polydactylism (tables 1 and 2). Four other cases (Keizer and Schilder, 1951, Debré et al, 1952a, Debré et al, 1952b, and Gallagher et al, 1953) which have been reported as examples of the syndrome are lacking in one or more of the minimal requirements and consequently have been omitted from our analysis. Table 2 presents the main clinical features of chondroectodermal dysplasia as found in twelve cases—the seven from the literature and the five of the present report.

The affiiction is not necessarily incompatible with good health. Most of the patients have passed childhood and three are now in their late teens. Intelligence has been reported as being within normal limits in nine cases. Weller (1951) and Gatto (1951) reported that their patients were mentally backward. One of the twins reported above is a microcephalic imbecile. On the other hand, McIntosh's original patient is now a university graduate.

No ethnic predisposition exists, for in the twelve cases seven different ethnic groups are represented, namely Jewish, English, Dutch, Turkish, Italian, Irish and French (table 1).

It may be seen from table 2 that the most constant features of the Ellis-van Creveld syndrome are 1) chondrodysplasia, 2) a sixth finger on the ulnar side of each hand, and 3) defective teeth and nails. Congenital heart disease, the fourth feature of the syndrome as originally described by Ellis and van Creveld (1940), has been recorded in five of the twelve collected cases. Sparsity of the hair of the head (cases 3 and 7), of the eyebrows (cases 3, 9 and 10), of the axillae (case 5), of the pubis (cases 5 and 11), and of the body generally (cases 2 and 4) has been reported; however, the feature is never severe, and is inconstant, since in four patients (cases 1, 6, 8, 12) the hair is normal in amount and distribution. Ellis and van Creveld (1940) found no microscopic abnormality of the hair in the two patients (cases 2 and 3) who had "abnormally sparse" hair.

Pedal polydactyly was present in one of our cases and has been reported in one other case (Caffey, 1952). Reduction or obliteration of the sulcus between the upper lip and gum was a feature of nine of the ten patients where a specific statement is made concerning it. It appears, therefore, that reduction or ab-

TABLE 2. SOME CONSTANT AND INCONSTANT CLINICAL FEATURES OF CHONDROECTODERMAL DYSPLASIA

SIBSHIP AND CASE	CHONDRODYSPLASIA		POLYDACTYLY		ECTODERMAL DYSPLASIA			CONGENITAL HEART DISEASE	REDUCED OR ABSENT SULCUS	INTELLIGENCE	OTHER ABNORMALITIES
	Extremities short	Trunk not affected	Hands	Feet	Teeth	Nails	Hair				
I–1	+	+	+	—	+	+	Normal	No	No	University graduate	Lordosis; strabismus
II–2	+	+	+	—	+	+	Fine, fair and sparse	Interventricular septal defect	Upper	Normal for age	—
III–3	+	+	+	—	+	+	Fine, fair and scanty on head and eyebrows	Interventricular septal defect	Upper	Normal for age	Penis small; cryptorchism
IV–4	+	+	+	—	+	+	Sparse	Interauricular septal defect	?	Mentally backward	—
V–5	+	+	+	—	+	+	No axillary or pubic hair	Septal defect	?	At 13 years mental age of 7	—
VI–6	+	+	+	+	+	+	Normal	No	Upper	Normal mental powers	—
VII–7	+	+	+	—	+	+	Scanty on scalp	Interventricular septal defect	Upper	Retarded?	(not expected to live)
VIII–8	+	+	+	+	+	+	Normal	No	Upper	Normal mentality	Epispadias
IX–9	+	+	+	—	+	+	Eyebrows thin	No	Upper	Normal mentality	Epispadias
X–10	+	+	+	—	+	+	Eyebrows thin	No	Upper	Normal mentality	—
X–11	+	+	+	—	+	+	Pubic hair sparse	No	Upper	Below average	—
X–12	+	+	+	—	+	+	Normal	No	Upper and lower	Imbecile	Microcephaly; epilepsy; cataracts

sence of the upper sulcus may be a more constant feature of this syndrome than congenital heart disease.

In the eight families where a statement regarding siblings of the propositae is given, there are nine sisters, seven brothers, three siblings of unstated sex, and three miscarriages. Of the nineteen siblings of the propositae seventeen were unaffected and two were affected. The number of families involved is too small to merit presentation of the statistical techniques for sibling analysis, but it is clear that the number of actual recurrences (2.00) is perfectly compatible with that expected (3.06) on the basis of simple recessive inheritance (Macklin, 1938).

In three of the ten families parental consanguinity was reported. This is probably a much higher frequency than that in the population, generally estimated as around one per cent (Stern, 1949). Even if the frequency in the population is taken as two per cent, the probability of drawing three cases of consanguineous parentage out of ten by chance is 1/1250 (Lamy, 1952). It can reasonably be concluded, therefore, that the frequency of consanguinity in the present series is not due to chance. The finding of an elevated consanguinity rate in the parents of children with a rare disease is evidence for recessive inheritance of that disease (Fraser, 1951).

In view of these findings it was felt justifiable to advise the parents of sibships VIII and IX (table 1) that there may be a twenty-five per cent risk of recurrence of the disease in any subsequent sibling.

SUMMARY

1. Five new cases of the Ellis-van Creveld syndrome are presented. One of these is a sporadic case, two occurred in brother and sister, and two in dizygotic twin brothers.

2. The five new cases are combined with the seven previously reported and a genetic analysis is made.

3. On the basis of the recurrence of the condition in siblings in two of the ten families, and the high incidence of parental consanguinity (3/10), an autosomal recessive mode of inheritance is suggested.

ACKNOWLEDGMENTS

We would like to express our sincere thanks to Dr. J. Scott Dunbar of the Department of Radiology, The Children's Memorial Hospital, and to Dr. R. G. Fraser of the Department of Radiology, Royal Victoria Hospital for permission to publish the genetic aspects of these cases; to Dr. M. Kissane of Malone, New York for providing us with detailed information on the past history of the twins; to Dr. J. S. L. Browne for permission to publish the case histories of the twins; to Dr. J. G. Petrie for permission to publish case 8, and to the Federal-Provincial Public Health Fund for financial support.

ADDENDUM

Since this paper was written, two additional cases of the Ellis-van Creveld syndrome occurring in the same sibship, have come to our attention. The proband is an eight-year-old girl with the characteristic findings of chondroectodermal dysplasia and polydactyly. In addition, she has a grade III systolic murmur in the pulmonary area, suggestive of congenital heart disease. The parents (M = 40; F = 44), who are fourth cousins, three older sisters (19, 14 and 12), and three older brothers (18, 16 and 15) are alive and free from any congenital defects. The seventh pregnancy terminated as a miscarriage at forty days. This was followed by a male child who died at three months, and was was said to be "exactly the same as the patient" in that he had the extra finger on each hand and shortening of the limbs.

REFERENCES

Caffey, J. 1952. Chondroectodermal dysplasia (Ellis-van Creveld disease). *Am. J. Roentgenol.* 68: 875.

Debré, R., Lamy, M., Aussannaire, M., Jammet, M. L., and Frézal, J. 1952a. Syndrome d'Ellis-van Creveld. *Arch. fr. de Péd.* 9: 65.

Debré, R., Lamy, M., Minkowski, A., and Grumbach, R., 1952b. Syndrome d'Ellis-van Creveld chez un nouveau-né décédé le premier jour. *Arch. fr. de Péd.* 9: 1055.

Dunbar, J. S., and Fraser, R. G. 1954. In preparation.

Ellis, R. W. B., and van Creveld, S. 1940. A syndrome characterized by ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis. *Arch. Dis. Child.* 15: 65.

Fraser, F. C. 1952. Consanguinity and its significance in the family history. *Can. Med. J.* 66: 258.

Gallagher, E. J., MacGregor, M. E., and Israelski, M. 1953. Chondrodystrophy with ectodermal defects. *Arch. Dis. Child.* 28: 14.

Gatto, I. 1951. Ellis-van Creveld Syndrome. *Helv. paed. Acta* 6: 437.

Keizer, D. P. R., and Schilder, J. H. 1951. Ectodermal dysplasia, achondrodysplasia, and congenital morbus cordis. *Am. J. Dis. Child.* 82: 341.

Lamy, M. 1952. *Précis de Génétique Médicale.* Paris. G. Doin and Cie.

Macklin, M. T. 1938. Methods of correcting pedigree data. *J. Hered.* 29: 295.

McIntosh, R. 1933. "*Holt's Diseases of Infancy and Childhood.*" Tenth Edition. D. Appleton-Century Co., N. Y., p. 362.

Stern, C. 1949. *Principles of Human Genetics.* Freeman and Co., San Francisco.

Weller, S. D. V. 1951. Chondro-ectodermal dysplasia (Ellis-van Creveld syndrome). *Proc. Roy. Soc. Med.* 44: 731.

Blue Sclerae, Fragilitas Ossium, Arachnodactyly and Deafness in an Indian Family

PHILLIP V. TOBIAS

Department of Anatomy, University of the Witwatersrand, Johannesburg

IT HAS BEEN KNOWN since the beginning of the century that blue sclerae may be associated with fragility of bones and that the symptom-diad is hereditary (Spurway 1896, Eddowes 1900). A further component of the syndrome is deafness, generally otosclerotic in origin (Bronson 1917), while various families show, in addition, hyper-extensibility of joints, poor dental development, arachnodactyly and a variety of other defects.

This hereditary condition is uncommon in natives of India. Gray (1935) described a single case of multiple fractures in an Indian, while Harnett (1934) reported the condition in two Bengali brothers and their mother, and in an Anglo-Indian (Eurasian) girl and her younger brother and sister.

When the author was informed that a family of Muslim Indians living in South Africa included a number of cases of blue sclerae, it was deemed of sufficient interest to investigate the family. The present note places on record the results of this study. The author is indebted to Dr. I. Kaplan for bringing the cases to his attention and for carrying out clinical examinations on the available members of the family.

OBSERVATIONS

The family hails from Bombay, where both Mr. and Mrs. P. and their older children were born. The younger children were born since the family migrated to South Africa. Mr. and Mrs. P. (V-10 and V-14) and all their living offspring (VI-6, 7, 9, 11, 13, 15, 17) and grandchildren (VII-4 and VII-5) were directly examined. The first examinations were carried out in February–March 1951 by Dr. I. Kaplan together with the author; a second series of examinations was made by the author in November 1953. Between these two dates, the two grand-daughters, children of VI-7, were born. A detailed family history was elicited. Mr. P. is the headmaster of a school and his reliability as a witness, coupled with the intelligent understanding and excellent memory of his wife, made it possible to compile a pedigree of almost 60 persons (fig. 1).

Mrs. P. (V-14), 52 years of age, is the mother of the affected sibs. She is a short, obese, middle-aged woman, who has been completely deaf since the age of 28. Her sclerae are china blue in colour and provide a most attractive contrast with her pale brown skin. She has a well-marked arcus senilis, which has been present at least since she was first examined three

Received January 14, 1954.

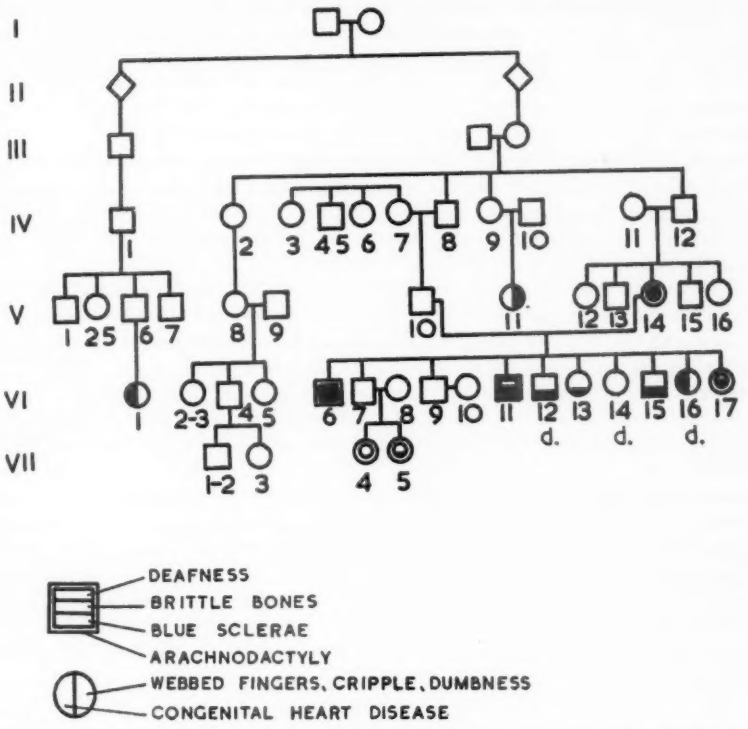

FIG. 1. Pedigree of Indian family with deafness, brittle bones, blue sclerae, and arachnodactyly

years ago. Starting at the age of about 12, she has suffered a number of fractures of the hips and arms and a series of sprains and dislocations in her lower limbs. There are deformities from mal-united fractures on her wrists and fore-arms, while her skull is characterised by prominent bosses in the parieto-temporal region. Her fingers and toes are long and tapering. There is no increased laxity of the joints. Neither her parents nor her brothers and sisters manifested blue sclerae or brittle bones. However, her first cousin (V-11), her father's younger sister's child, was crippled and dumb from birth and had webbed fingers. This child began to walk at 10 years of age but died soon after, without having broken any bones. Mrs. P's third cousin (V-6) the grandson of her paternal grandmother's first cousin, had a daughter (VI-1) who died of congenital heart disease.

Mr. P. (V-10) is first cousin to his wife. He is healthy and normal in appearance, bony structure and hearing.

Cassim (VI-6), the eldest son of Mr. and Mrs. P., is 33 years of age. He has blue sclerae, fragile bones and is completely deaf. He first noticed an impairment of his hearing in India at the age of 17. Despite treatment, the deafness progressed slowly, until, when examined in 1951, at the age of 30, he could hear with a hearing aid on the right side only. When seen more recently (November 1953), he could hear no sounds whatever, even with the aid of an appliance. Otological examination revealed nerve deafness as the predominant feature and it was concluded that both his auditory nerves have undergone degeneration. When 3

years old, he suffered his first fracture. Altogether, he has fractured leg-bones thrice, ribs twice, his wrist once, his jaw once and his knuckles once, eight fractures in all. There is slight winging of the scapulae. His fingers and toes are very long and slender, while his lower limbs are long in relation to the size of his trunk. His teeth are not crowded nor irregular. He has prominent parietal and occipital eminences. He started going bald prematurely at 22 and to-day has very scanty and short hair. There is a distinct arcus senilis.

Goolam (VI-7), aged 27, is unaffected in respect to bones, ears and eyes, except that there is a commencing arcus senilis. His skull is not abnormally bossed. His wife (VI-8) is normal in these features. They have two daughters, Souriya (2½ years) and Yasmin (7 months). Both children show moderate arachnodactyly, while Yasmin (VII-5) has distinctly blue sclerae, although both her parents and her elder sister have white sclerae.

Yussuf (VI-9), aged 24, is normal. His teeth are crowded and irregular. He married in 1953 and has no children to date.

Jakoob (VI-11), 21 years of age, has blue sclerae, brittle bones and arachnodactyly. He fractured his right elbow at the age of 10 or 11, his left ankle at 14 and his right fourth metacarpal some time later. The last bone has "collapsed" on two subsequent occasions. His hearing is intact. He is round-shouldered and his scapulae are slightly winged. His arms and legs are long, his fingers and toes long and tapering. His teeth are regular and are not crowded.

A male child (VI-12) showed blue sclerae until his death at3 1 months.

Fatima (VI-13), 17 years old, has bluish sclerae, crowded and irregular teeth, round shoulders and winged scapulae. There is a marked occipital protuberance on her skull and she has an early arcus senilis.

Ismail (VI-15), aged 11 years, has bluish sclerae and a commencing arcus senilis is clearly detectable. So far, he has not suffered any fractures. He is round-shouldered and has winged scapulae. His fingers are rather long, his teeth regular though carious. He has prominent skull-bosses, low down in the mastoid temporal region.

A female child (VI-16) who died at 6 weeks showed a generalised cyanosis. The exact nature of her complaint could not be determined, but a congenital heart defect may be indicated.

Zabeida (VI-17), the youngest child, is 6 years of age. Her sclerae are deeply and vividly blue, but she has no sign of an arcus. At 4, she fractured her clavicle. So far, this has been her only fracture. Her fingers are somewhat long and tapering, her scapulae winged, her teeth crowded, irregular and grossly carious. There is a slight inversion deformity of her left ankle and foot. There is marked asymmetrical parietal bossing.

DISCUSSION

The inheritance is clearly of dominant type, although the consanguineous union between Mr. and Mrs. P. might at first suggest recessiveness. There is, however, one "skip," namely Goolam (VI-7), who is normal in respect of the main symptom-triad, yet transmits the tendency for blue sclerae to his younger daughter (VII-5) and for arachnodactyly to both daughters. Penetrance is thus incomplete. Ottley (1932) figures a similar "skip" in her pedigree, an unaffected sister of the proposita transmitting the tendency for blue sclerae to her son. The complete failure of penetrance, even in the mildest form of the syndrome, viz. blue sclerae, has been reported, too, in isolated pedigrees by

Conard and Davenport (1915—quoted by Gates 1946), Holcomb (1931) and McGregor (1935).

A noteworthy feature in the present pedigree is the apparent new mutational origin of the symptom-triad in the germ-cells of either of Mrs. P's parents. Both of her parents were normal and there is no record or memory of the condition in their forebears, nor has the genetic tendency been handed down to other branches of the family e.g. the families of Mrs. P's aunts (IV-2 and IV-9). On the other hand, the younger aunt (IV-9) had a child who was crippled, dumb and had webbed fingers (V-11). In no previous pedigree available to the author have webbed fingers been reported in the same pedigree as brittle bones and blue sclerae, although *syndactyly* is described by Schinz et al. (1950—quoted by Hernberg 1952) as an associated condition. If the mutation to brittle bones arose in either of Mrs. P's parents, it is unlikely to be linked in any manner with the etiology of the webbed fingers; on the other hand, if the mutation arose in the germ-cells of either of Mrs. P's paternal grandparents, and failed to penetrate in Mrs. P's father, then it is possible that similar changes in the germ-cells of either grandparent might have accounted for the mutational origin of webbed fingers and the other anomalies in V-11.

Whether it occurred in the IIIrd or the IVth generation, the sudden appearance of these characteristic symptoms in Mrs. P., following several unaffected generations, strongly suggests a new mutation. The sudden apparent mutational origin of the condition has often been reported before and Gates (1946) comments that "This syndrome appears to occur frequently as a fresh mutation."

Even more remotely associated with the symptom-triad than webbed fingers is the occurrence of congenital heart disease in the daughter of Mrs. P's third cousin (V-6). The direct genetic relationship between this branch of the family and the branch with blue sclerae is through generation I, i.e. four generations before blue sclerae became manifest. It is unlikely, therefore, that congenital heart disease is linked in this pedigree with the symptom-triad. The possibility exists, however, that VI-16, the second youngest child of Mrs. P., may have had congenital heart disease. Only one previous reference to morbus cordis in association with blue sclerae and other anomalies has been traced, namely the pedigree published by Voorhoewe (1918): in this family, a woman with blue sclerae had a daughter with a congenital deformity of the heart and two out of six other children possessing blue sclerae.

In the P. family, as in others previously published, the expression of the three main symptoms is very variable. All of the 8 affected individuals show blue sclerae; 4 have in addition a tendency to fracture readily; of these, 2 are completely deaf. These figures coincide with those of Fraser (1934), namely, blue sclerae in 90–100% of affected persons; brittle bones with fractures in 50%

TABLE 1. CHARACTERISTICS OF INDIAN FAMILY

NAME	AGE	NO.	BLUE SCLERAE	FRACTURES		DEAFNESS		ARACHNODACTYLY	ARCUS SENILIS	DENTAL CROWDING	SKULL BOSSING	WINGED SCAPULAE	SKIN AFFECTIONS
				Age of 1st Fracture	Total No.	Yes/No + −	Age of Onset						
Mrs. P.	52	V-14	+	±12	±6	+	?	+	+	−	+	+	+
Cassim	33	VI-6	+	±3	8	+	Totally from 28 17 Totally from 32	+	+	−	+	±	+
Goolam	27	VI-9	−	−	−	−	−	−	±	−	−	−	−
Souriya	2½	VII-4	−	−	−	−	−	+	−	−	±	−	−
Yasmin	½	VII-5	+	−	−	−	−	+	−	−	±	−	−
Yussuf	24	VI-9	−	−	−	−	−	−	−	+	−	−	−
Jakoob	21	VI-11	+	10–11	5	−	−	+	±	−	±	+	+
Boy	dec.	VI-12	+	−	−	−	−	?	?	?	?	?	−
Fatima	17	VI-13	+	−	−	−	−	−	±	+	+	+	+
Ismail	11	VI-15	+	−	−	−	−	−	±	−	+	+	+
Girl	dec.	VI-16	?	−	−	−	−	?	?	?	?	?	−
Zabeida	6	VI-17	+	4	1	−	−	+	−	+	+	+	−

and deafness in 25%. These figures may still be upset if some of the younger affected sibs develop deafness.

A wide variety of conditions may be associated with this symptom-triad and, it has not yet been determined whether these are due to a cluster of related mutations or to the pleiotropic effects of a single mutation. Attempts to link all the manifestations on a developmental physiological basis have not been successful, although it seems that the syndrome focusses itself upon ectodermal and mesodermal derivatives. The present family manifests both previously reported related characteristics and some new ones. Table 1 summarises the findings in the various members of the family.

An interesting feature of this family is that some associated conditions crop out in unaffected or very slightly affected individuals This may be part of the extreme variation in expressivity or may reflect the action of several closely linked mutant loci.

Moderate arachnodactyly occurs in all four of the affected ones with fragilitas ossium; in addition, the two members of generation VII show arachnodactyly, one with no other signs or symptoms, the second with blue sclerae. Ellis (1931) reported arachnodactyly in a family combined with fragilitas ossium and blue sclerae, while Schinz et al. (1950—quoted by Hernberg 1952) quotes spider fingers as a condition often associated with the symptom-triad.

Abnormal skull bossing, chiefly in the parietal and occipital regions, is

present in five members of the family, all of whom have blue sclerae and are in other ways affected. The parietal bossing is not the high pedomorphic or infantile variety which is typical of the yellow-skinned Bush-Boskop folk of Southern Africa; instead, it is low, often being at the level of the temporal squame and, in at least one instance, the mastoid temporal, and markedly and unusually asymmetrical. Such abnormal bossing is a well-known concomitant of the symptom-triad (Ottley 1932) and sometimes gives a characteristic flattened appearance to the skull, with well-marked parieto-temporal and occipital bossing, the "crâne à rebord" of Apert (1928). In some cases, according to Ottley and Apert, the temporal bulging is so marked that the upper part of the pinna is pushed outwards and folded upon the lower part.

Dental crowding and irregularities occur in three children, one of them, Yussuf, seemingly otherwise unaffected. Apert (1928), Ottley (1932) and others have reported dental defects in pedigrees of blue sclerae and brittle bones. In view of the extreme variation in expressivity, does the dental crowding in Yussuf reflect a very slight expression of the same genetic change?

This family does not manifest the usually associated condition of hyperlaxity of joint-ligaments, but Mrs. P. suffered numerous sprains and dislocations when younger.

Another classical associated finding is a well-marked and premature arcus senilis. Both Mrs. P. and her eldest son, Cassim, show this feature. In the second son, Goolam, who is otherwise unaffected (although he transmits the mutant genotype to his daughters), there is a commencing arcus senilis at 27 years of age. Most surprising is the definite indication of a commencing arcus in Jakoob (21), Fatima (17) and even Ismail (11). Zabeida, aged 6, is however free from this sign.

A peculiarity of this family is the association with round shoulders and winged scapulae. Six members of the family, both affected and unaffected individuals, show this feature. Although not previously combined with blue sclerae, winged scapulae have been associated with arachnodactyly, as indeed has congenital heart disease. There may be a developmental link through a dystrophy of the mesoderm (Gates 1946).

The P. family is especially liable to skin affections, an association not previously encountered in the literature (except that the case reported by Eddowes in 1900 suffered from eczema). Mrs. P. and Jakoob suffer from phrynoderma, Cassim from premature baldness and lichen planus, Fatima from dermatosis and Ismail from cutaneous ulcers contracted on a visit to India. In this apparent ectodermal weakness, there may be a phenogenetic link with the unusually thin type of sclera and cornea which Buchanan (1903) demonstrated in one case of blue sclerae, a thinning which is sometimes held responsible for the blue coloration.

All the manifestations described may be grouped into two large categories: mesodermal effects and ectodermal effects.

Mesodermal Effects	*Ectodermal Effects*
Brittle bones	Blue sclerae
Arachnodactyly	Premature arcus senilis
Otosclerotic deafness	VIII nerve deafness
Defective teeth (dentine)	Defective teeth (enamel)
Skull bossing	Skin affections
Winged scapulae	Premature baldness

The most striking group of features comprises the mesodermal bony defects, which manifest themselves in the osseous system generally and, specifically, in the skull, including ear ossicles and teeth, the shoulder-girdle and the extremities. According to Bauer (1920—quoted by Ottley 1932), the muscles, the urogenital system and the adrenal cortex are unaffected; he concluded that only the mesenchymal part of the mesoderm is involved. Other cases of fragilitas ossium failed to confirm Bauer's mesenchymal theory. Muscular changes and lymphocytosis are additional mesodermal changes reported (Ottley 1932). The ectodermal defects are closely related to the mesodermal e.g. defective enamel formation occurs in some and poor dentine formation in others (Jeckeln 1931); primary nerve deafness in one group, otosclerosis in another. In the cutaneous weaknesses, the defect may as soon reside in the mesodermal dermis as in the epidermis. As far as the scleral and corneal effects are concerned, in contrast with Buchanan's finding that the sclerae are abnormally thin, thus allowing the uveal pigment to show through, Bronson (1917) found the sclerae to be of normal thickness, although deficient in calcium and hence, unduly translucent. Buchanan's view is nevertheless quoted to explain blue sclerae in a recent work on ophthalmology by Wolff (1953). Further confusion exists in the opinions on the histopathology of the bony and dental weaknesses. For example, Looser (1905—quoted by Ottley 1932) holds that osteoclastic activity is increased, while other authors contradict this. Ottley (1932) has reviewed many conflicting opinions on the etiology and pathology.

Authors are not even unanimous on the distinctness of the conditions osteogenesis imperfecta congenita (Vrolick's disease) and osteogenesis imperfecta tarda (Lobstein's osteopsathyrosis, fragilitas ossium with or without blue sclerae) (Riesenman and Yater 1941, Rosenbaum 1944). A still more difficult problem is to decide whether all cases of hereditary fragilitas ossium may justifiably be lumped into a single disease entity: there are families with and families without blue sclerae, with and without hyperextensibility of joints, with and without deafness. The diversity of the main effects may suggest a hitherto unsuspected embryological connection between bone- and sclera-formation; alternatively, this may be a case of true pleiotropism or of a tightly

linked cluster of mutant loci. It is clear that much work remains to be done on the exact nature of the pathological effects and that such genetic schemes as that of Seedorff (1949—quoted by Hernberg 1952) must at this stage be tentative, if not premature. Only by the elucidation of the embryogeny, pathogenesis and morbid histology of the syndrome can a rational explanation be offered of the genetic and embryological connection between the varied manifestations: towards this end, it is hoped that this study may contribute, by placing on record additional associated conditions and bringing nearer an appreciation of the totality of phenotypic effects occurring in this genotypic derangement.

SUMMARY

A family showing the hereditary symptom-triad of blue sclerae, brittle bones and deafness has been described.

Heredity is dominant with one "skip."

The condition has apparently arisen in this family as a fresh mutation.

Expressivity is very variable: all 8 affected persons have blue sclerae; 4 of these show a tendency to fracture easily; 2 of the latter group are, in addition completely deaf.

Arachnodactyly, dental crowding and irregularities, well-marked and premature arcus senilis, unusual skull bossing and other bony deformities and a tendency to sprains and dislocations, are previously reported associated anomalies present in the family.

Winged scapulae and a tendency to skin affections are two conditions not previously known to be associated with the symptom-triad.

Some of the associated conditions are shown by otherwise unaffected members of the family.

There is a more remote association in this pedigree with dumbness, webbed fingers, a crippling deformity and congenital heart disease, and a nearer connection with another possible case of morbus cordis.

The grossest effects are in tissues of mesodermal origin; while the ectodermal effects are mainly closely related to the mesodermal defects.

REFERENCES

ALPERT, E. 1928. Les Hommes de Verre. *Presse Médic.* 36: 805.

BRONSON, E. 1917. On fragilitas ossium and its association with blue sclerotics and otosclerosis. *Edinb. Med. Journ.* 18: 240.

BUCHANAN, L. 1903. Case of congenital maldevelopment of the cornea and sclerotic. *Trans. Ophth. Soc. U. K.* 23: 267.

EDDOWES, A. 1900. Dark sclerotics and fragilitas ossium. *Brit. Med. J.* 2: 222.

ELLIS, R. W. B. 1931. Four cases of fragilitas ossium and blue sclerotics. *Proc. Roy. Soc. Med.* 24: 1054.

FRASER, I. 1934. Fragilitas ossium tarda. *Brit. J. Surg.* 22: 231.

GATES, R. R. 1946. *Human Genetics*. The MacMillan Co., New York.
GRAY, G. D. 1935. Defective ossification. *Brit. Med. J.* 2: 14.
HARNETT, W. L. 1934. Two cases of osteogenesis imperfecta with blue sclerotics in natives of India. *Brit. J. Surg.* 22: 269.
HERNBERG, C. A. 1952. Fragilitas ossium hereditaria with blue sclerae and its treatment with androgens and oestrogens. *Acta Med. Scand.* 141: 309.
HOLCOMB, D. Y. 1931. A fragile-boned family. *J. Hered.* 22: 104.
JECKELN, E. 1931. Systemgebundene mesenchymale Erschöpfung. *Virch. Arch. path. Anat. Phys.* 280: 351.
MCGREGOR, H. G. 1935. Brittle bones with blue sclerotics in 15 members of a family. *Guy's Hosp. Rep.* 85: 356.
OTTLEY, C. M. 1932. Osteopsathyrosis (Lobstein's disease). *Arch. Dis. Childhood* 7: 137.
RIESENMAN, F. R. AND YATER, W. M. 1941. Osteogenesis imperfecta: its incidence and manifestations in 7 families. *Arch. Int. Med. 67:* 950.
ROSENBAUM, S. 1944. Osteogenesis imperfecta and osteopsathyrosis. *J. Pediatr.* 25: 161.
SPURWAY, J. 1896. Hereditary tendency to fracture. *Brit. Med. J.* 2. 844.
VOORHOEVE, N. 1918. Blue sclerotics in connection with other hereditary or congenital abnormalities. *Lancet.* 2: 740.
WOLFF, E. 1953. *Diseases of the Eye.* Cassell & Co. Ltd., London.

The Mutation Rate of the Rh-Loci—a Critical Review

FRIEDRICH VOGEL

Max Planck-Institut für vergleichende Erbbiologie und Erbpathologie
Berlin-Dahlem

IN THEIR PAPER on the mutation rate of fibrosis of the pancreas, Goodman and Reed (3) have given an estimate of the mutation rate for the Rh-loci by means of the indirect method developed by Haldane (4) and ordinarily used for dominant and sex-linked recessive genes. They found a mutation rate of 5.1×10^{-4} for the Caucasian population of the U. S. In view of the great practical importance of the Rh-loci, the confirmation of a mutation rate of this magnitude would be of fundamental importance. It therefore seems to be justified to analyse somewhat more exhaustively the premises on which the estimate is based.

In his indirect method, Haldane derives the mutation rate from the selective value of an allele presupposing an equilibrium between selection and mutation which tends to re-establish itself after any disturbance. Such an equilibrium has in fact been shown to exist for all kinds of selection so far examined.

As to the Rh-loci, however, the situation is different. Here selection works against heterozygotes. Haldane (5) has given an approximation formula:

$$\Delta q = sq^2(1 - q)(q - \tfrac{1}{2}), \qquad (1)$$

where s = selective value, q = frequency of the *rh* allele, and Δq = change of q per generation.

This formula holds true as long as s is small. As may easily been seen, this function crosses the zero line at three points: $q = 0$; $q = 1$; $q = \frac{1}{2}$, the first two corresponding to a stable equilibrium, the third to an unstable one. Hence, the more frequent allele tends to increase in frequency at the expense of the less frequent one. From this formula Haldane concludes that the present Caucasian U. S. population cannot be in a state of equilibrium for the *Rh* gene since the less frequent *rh* gene is diminishing more and more. He assumes that the population has originated by a break up of isolates with predominantly *rh* and *Rh* respectively, or else, as he concludes, the influence of an additional biological factor would be necessary.

Goodman and Reed, on the other hand, prefer to assume a permanent replacement of the lost genes by mutation. They calculate the mutation rate by introducing the empirical data of q into the equation (1). In the present

Received January 22, 1954.

author's opinion, this would lack exactness even if the basic considerations could be accepted. By their method of calculation they can obtain but the frequency of $u(1 - q)$ (u = mutation rate). Using their figures, this would lead to: $u = 8.4 \times 10^{-4}$.

As for the joint effects of selection and mutation, we must add the right sides of the equations:

$$\Delta q = u(1 - q) + sq^2(1 - q)(q - \tfrac{1}{2}) \qquad (2)$$

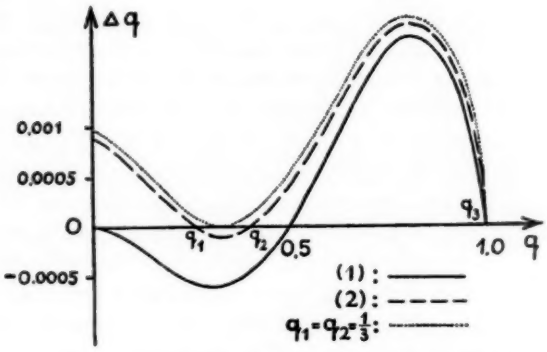

FIG. 1. Curve (2) using Goodman's and Reed's data

We see: a.) Both curves show an unstable equilibrium, (1) at $q = 0.5$; (2) at $q = 0.39$; b.) Beyond this, in (2), there appears an equilibrium at $q = 0.28$. This equilibrium is stable as long as q does not exceed the value 0.39. The question seems thus to be justified: Did such an equilibrium become established in the American population? This means: Does q_1 amount to 0.39? In that case, we should have to deal with a still higher mutation rate.

Obviously, the values of q_1 and q_2 tend to become equal with increasing values of u. In case they are equal, equation (2) has a minimum at $\Delta q = 0$. Hence, like Δq, its first derivative

$\Delta(q)' = 0$. Eliminating u, we find:

$$q = \tfrac{1}{3} \text{ (and: } \quad q = 1) \qquad (3)$$

and introducing this value into (2):

$$(4) \qquad u = \frac{s}{54}$$

This means: For all concrete data of s and u, a stable equilibrium is possible only when $q < \frac{1}{3}$, and accordingly, an unstable one when $q > \frac{1}{3}$.
Moreover: An equilibrium of any kind or a preponderance of selection is possible only when: $u < \frac{s}{54}$.

Applying this to the concrete data examined by Goodman and Reed, this means: a.) No stable equilibrium can be established at q = 0.39. b.) The existence of an unstable equilibrium seems to be most unlikely since 1.) The least effect of genetic drift would immediately destroy it. 2) The way it would become established remains unknown. (Neither Li (7) nor Hogben (6), who believe such an equilibrium to be possible, give an answer to this question.) 3.) It can be taken for granted that the Caucasian population of the U. S. is a mixture of populations with different Rh frequencies. Hence, any unstable equilibrium would surely have been destroyed.

On the other side, the possibility of a stable equilibrium may be discussed for populations with $q < \frac{1}{3}$. In order to appraise this possibility, knowledge of the following data would be necessary: a.) The rate of q, b.) The number and size of isolates in the population concerned, c.) The intensity of s. (0.05 is a rough and simplified estimate, which neglects the variability in reproduction as well as the various qualities of the Rh subgroups).

On the basis of such data, it would not be too difficult to calculate the time in which q_1 is likely to exceed q_2. This time is comparable to the number of generations necessary for the establishment of an equilibrium as calculated by Haldane's integration formula. Nevertheless, conclusive information about the mutation rate of the Rh loci could only be obtained by observing mutations directly, especially because the rate of back mutations is not considered. Moreover, the effects of illegitimacy etc. may seriously falsify the result.

Fisher and others (1) have questioned whether considerations of this kind can really be applied to human populations. Recent research, however, has shown that Rh-negative Negro women of Baltimore had a significantly lower number of children that Rh-positive ones. On the other hand, the Caucasian population of Baltimore did not show any such difference: In a population practicing birth control dead children tend to be replaced (Glass, 1950).

APPENDIX

Prof. J. B. S. Haldane, to whom I am very grateful for his comments, kindly informs me that the calculations of Goodman and Reed (and consequently my own, too) are based upon a formula now regarded as obsolete. It appears that there is but a small number of *dd*-mothers who produce a high concentration of antibodies during a single pregnancy. Thus the danger to *Dd*-children from *dd*♀ × *DD*♂ matings is much higher than that for babies from *dd*♀ × Dd♂ matings. In a population with

$$x\,DD + 2y\,Dd + z\,dd\text{, where } x + 2y + z = 1,$$

$$x + y = p,$$

$$y + z = q$$

the following generation will prove to show:

$$x' = \frac{p^2}{1 - z(Sx + sy)}; \quad y' = \frac{pq - \frac{1}{2}z(Sx + sy)}{1 - z(Sx + sy)}; \quad z' = \frac{q^2}{1 - z(Sx + sy)}$$

(S = selective value in *dd* ♀ x *DD* ♂ pregnancies)

(s = selective value in *dd* ♀ x *Dd* ♂ pregnancies)

There will be

$$q' = \frac{q - \frac{1}{2}z(Sx + sy)}{1 - z(Sx + sy)}$$

or:

$$\Delta q = q - q' = \frac{(q - \frac{1}{2})z(Sx + sy)}{1 - z(Sx + sy)} \qquad \text{(Haldane)} \quad (5)$$

The equation used above would be approximately correct if S = s, the correct formulation being:

$$\Delta q = q - q' = \frac{Sq'(2q' - 1)^2q^2}{2[2q' - 1 - 2S\{q' - q + q'(q' - 1)q^2\}]} \qquad \text{(Haldane)}$$

It is of importance that the above stable equilibrium in case of $q < \frac{1}{3}$ is also valid for $S \neq s$. Haldane proved this true for the case $s = 0$. (As S and s are small the formula may be simplified by neglecting the denominator and introducing $x = (1 - q)^2$; $y = q(1 - q)$; $z = q^2$).
Introducing the term $u(1 - q)$ and $q = \frac{1}{3}$ into the simplified form of the equation (5), there will be:

$$u = \frac{1}{54}(\frac{2}{3}S + \frac{1}{3}s) \qquad (4a)$$

Professor Haldane thinks it somewhat abstract to deal with mutations in one direction only but he also states that four arbitrary constants would have to be introduced, if we started considering mutations in both directions.

In the special case of equal mutation rates in both directions ($\Delta q = u(1 - 2q)$), an unstable equilibrium would be obtained if $q = 0.5$, a stable equilibrium at $0 < q_1 < 0.5$ and $1 > q_3 > 0.5$ respectively, whereby q_1 and q_3 could take any value between 0 and 0.5 and between 0.5 and 1 respectively, depending on S, s, and u. Considering the rate of back mutation, it would, of course, be possible to figure cases of a stable equilibrium with $q = 0.39$ the proof of which could be only made by observing the mutations directly.

(The author gratefully acknowledges mathematical advice given by cand. rer. nat. D. Strobel.)

REFERENCES

(1) FISHER, R. A. Quoted from: Race and Sanger. 1950. *Blood Groups in Man*. Oxford.
(2) GLASS, B. 1950. The Action of Selection on the Principal Rh Alleles. *Am. J. Human Genet.* 2: 269.
(3) GOODMAN, H. O., AND REED, S. C., 1952. Heredity of Fibrosis of the Pancreas. Possible Mutation Rate. Am. J. Human Genet. 4: 59.
(4) HALDANE, J. B. S., 1935. The Rate of Spontaneous Mutation of a Human Gene. *J. Genet.* 31: 333.
(5) HALDANE, J. B. S. 1942. Selection against Heterozygotes in Man. *Ann. Eugen.* 11: 333.
(6) HOGBEN, L. 1943. Mutation and the Rhesus Reaction. *Nature* 152: 721.
(7) LI, C. C. 1948. *An Introduction to Population Genetics*. Peking.

Sex Ratio of White Births in the United States During the Second World War

BRIAN MacMAHON AND THOMAS F. PUGH

Department of Environmental Medicine and Community Health, State University of New York, College of Medicine at New York City
and
Department of Epidemiology, Harvard University School of Public Health, Boston, Mass.

FROM EUROPEAN SOURCES there is a good deal of circumstantial evidence to support the belief that the proportion of males to females born increases during or immediately following times of war. The sex ratio increased in practically all the belligerent European countries during the First World War and in the succeeding two or three years. Complete data have not been collected for the period of the Second World War, but certainly in England and Wales a most marked increase occurred. During the years 1941–46 the English live birth sex ratio was the highest ever recorded in that country since the introduction of birth registration in 1841 (Lowe and McKeown, 1951).

No change in sex ratio was noted in the United States during the First World War (Metropolitan Life, 1939). This is hardly surprising, since, as the latter authors point out, "at most 4 per cent (of the United States population) was under arms at any time, and this only for a very short period, whereas in the principal European populations from 15 to 22 per cent were so mobilized, in most instances for the entire duration of the war." The Second World War, however, affected the social structure of the United States to almost as great an extent as some of the participating European countries, and if no change in sex ratio occurred in the United States it would certainly bring into question the validity of the generalization regarding sex ratio and war.

Two investigators have been unable to demonstrate significant variation in the sex ratio in the United States during the Second World War. They conclude respectively, that "there is no evidence in the recent experience of our country that boy babies increase significantly during war and immediate postwar periods" (Metropolitan Life, 1949), and "the sex ratio at birth does not consistently change as a direct influence of war either during the war years or immediately after" (McMahan, 1951). The sole basis for the latter statement is the alleged absence of such change in the United States during the Second World War. An assumption that variations in the sex ratio at birth may be produced by differential elimination of the sexes from the uterus in early fetal life (Lowe and McKeown, 1950), makes it quite conceivable that such varia-

Received January 25, 1954.

tions may be associated with the social upheavals which accompany war. Such an assumption does not imply that the sex ratio at conception undergoes variation, although, of course, such might be the case.

Material

Sources of data are the annual reports of birth statistics for the United States published formerly by the Bureau of Census, Department of Commerce, and latterly by the National Office of Vital Statistics, United States Public Health Service. In view of the inadequacy of reporting of Negro and other non-white births in the United States, our examination is confined to white births.

Examination of the data on white stillbirths reveals the long-term trend illustrated in figure 1. A similar trend for stillbirths in England and Wales was noted by Lowe and McKeown (1951). It is not our purpose to comment on this marked downward trend in stillbirth sex ratio but it is of interest to note that: (1) Stillbirths are grossly under-reported. The extent of this under-reporting is unknown. Baumgartner, Wallace, Landsberg and Pessin (1949) estimated that only 86% of third trimester fetal deaths occurring in New York City in 1943–45 were reported. Since New York City is one of the more satisfactory

Fig. 1. Sex ratio of white stillbirths, U. S. Birth Registration Area, 1922–49*

* Data on stillbirths by sex are not available prior to 1922.

areas of the United States in respect to completeness of birth reporting, it is clear that the deficiency measured over the country as a whole must be considerable. (2) Although we have been unable to find statistical evidence bearing on the problem, it seems possible that where reporting is incomplete, males may be reported more frequently than females. This supposition receives some support from the fact that non-white live births, reporting of which is also grossly deficient, have shown a similar fall in sex ratio, as judged by national statistics. (3) If in fact under-reporting were associated with a high sex ratio, an improvement in reporting over a period of time would lead to just such a trend in sex ratio as noted here.

Whether the decrease in white stillbirth sex ratio is the result of reporting difficulties or of more directly biological factors it is clear that a long term trend of such a marked nature is likely to obscure changes occurring during a relatively short time period. We have, therefore, limited our examination to livebirths. This is not ideal, since changes in the incidence or sex ratio of stillbirths will affect the sex ratio of total births, stillbirths having a higher sex ratio than livebirths. However, the changes in livebirth sex ratio to be noted in association with the Second World War are abrupt, occurring over a period of three or four years only, and it is difficult to believe that they are appreciably influenced by the long-term trends noted in stillbirths. No such abrupt change either in stillbirth rate or in stillbirth sex ratio occurred in these years. In addition, the contribution of stillbirths to total births is small.

LIVEBIRTH SEX RATIO

In figure 2 is illustrated the sex ratio of all white livebirths in the U. S. Registration Area since its inception in 1915. Sex ratios were generally high in the years 1915–1930, lower in the succeeding 10 years, and high in the five years 1942–46, falling again in 1947–49. The sex ratio in 1946 was the highest ever recorded and that in 1942 was equalled previously only once—in 1925. For the years 1942–46, the sex ratio was 51.481, higher than that for the combined remaining years (51.422) by 0.059 ± 0.016 (critical ratio 3.7), and higher than that for the remaining years in the 20 year period 1930–49 (51.406) by 0.075 ± 0.016 (critical ratio 4.7).

The statistical significance of these differences depends on the large number of births involved, the magnitude of the differences being small. In addition, as pointed out by the Metropolitan Life (1949) there is the suggestion of an upward trend in sex ratio in the pre-war years and the war-time increase may merely be a continuation of a pre-existent trend. However, the interpretation of the meaning of the observations should take into account at least two factors. Firstly, prior to 1933 the Birth Registration Area was constantly shifting its geographical boundaries as states were admitted to and dropped from the Area. It was frequently observed that newly admitted states had high sex ratios. This

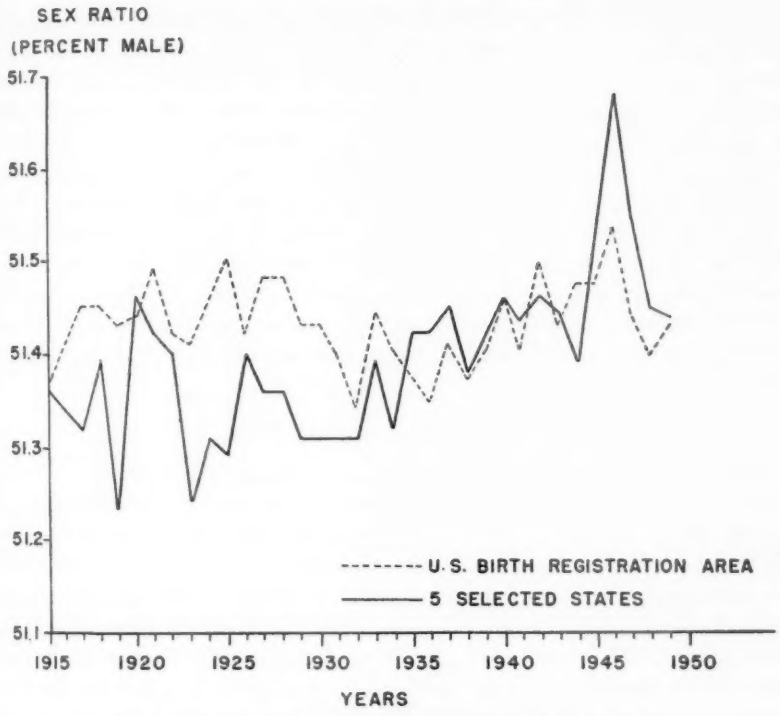

FIG. 2. Sex ratio of white livebirths in the United States, 1915–49

may also have its explanation in the greater completeness of male reporting in under-reported areas. Secondly, within the same geographical boundaries the proportion of births reported has increased progressively over the period considered. These factors may best be taken into account by examination of data for a constant geographical area, this area being selected for completeness of reporting.

There have been two nation-wide estimates of the completeness of livebirth reporting, in association with the censuses of 1930 (Whelpton, 1934) and of 1940 (Grove, 1943). In figure 2 is also given the white livebirth sex ratio in those states having 98% or more of white livebirths reported in both these investigations. There were five such states—Connecticut, Massachusetts, New Jersey, New York, and Rhode Island. The geographical area considered is not entirely constant since the figures exclude New Jersey and Rhode Island, two of the smaller states, for 1920 and the years previous.

The figure shows a high sex ratio in the last year of the war and the following two years. The ratio is again highest in 1946. The contrast between these years

and the preceding years is more marked than that seen for the whole Registration Area since (1) the sex ratio in 1946 is much higher than that for the Registration Area as a whole, and (2) limitation of the examination to these five states has eliminated the high ratios in the period 1915–1930. It is not possible to speculate with confidence on whether these differences are due to the intentional selection in terms of completeness of registration or to the resulting unintentional geographic selection of states lying on the Eastern seaboard. It is clear, however, that, at least in these five states, the end of the second World War saw a marked increase in the sex ratio of white livebirths. It is unfortunate that data for stillbirths by sex are not available separately for these states, but it is inconceivable that either the stillbirth rate or the stillbirth sex ratio experienced so marked and abrupt a change as would be necessary to account for the rise in livebirth sex ratio.

BIRTH RANK AND MOTHER'S AGE

Since sex ratio is believed to vary with age of mother and birth order of child (Ciocco, 1938), changes in the proportions of mothers at various ages and parities are the descriptive explanations most frequently put forward to account for changes in the sex ratio during war (Metropolitan Life 1939; Martin, 1943). We have shown elsewhere, however, that age of mother is without influence on sex ratio when account is taken of the association between maternal age and birth order (MacMahon and Pugh, 1953). It is unlikely, therefore, that sex ratio will be affected by changes in distribution of births by maternal age independent of birth order. The possibility remains that changes in birth order distribution associated with war may influence sex ratio, although in England and Wales such changes were insufficient to account for the observed changes in sex ratio (MacMahon and Pugh, 1953).

Sex ratios by birth rank are not available for the United States for the years immediately prior to 1942, and the question must be examined indirectly. Even for the years subsequent to 1942, the data are not available for individual states and the examination must be confined to the data presented for the United States as a whole in which the period 1942–1946 showed the highest sex ratio. Sex ratio is highest in first births and decreases with advancing birth order. The percentages of first births during 1942–46 and in the preceding five years, 1937–41, were almost identical (38.31% and 38.86% respectively). However, there was a rather lower percentage of births of birth ranks 6 and over in the period 1942–46 than in 1937–41 (7.49% as against 10.02%). If the sex ratios of white livebirths by birth rank for 1942–46 are applied to the known numbers of births in each birth rank in the preceding five years (1937–41), an expected number of male births is obtained which, on addition and application to the total number of births in the same years, gives an expected white livebirth sex ratio for 1937–41 on the assumption that sex ratios of individual birth ranks

TABLE 1. SEX RATIOS OF WHITE LIVEBIRTHS BY BIRTH ORDER, 1942–49

YEAR	BIRTH ORDER			
	1	2	3	4 & over
1942	51.66	51.47	51.40	51.21
	(1,014,372)	(614,047)	(304,780)	(432,000)
1943	51.59	51.49	51.32	51.11
	(945,312)	(694,414)	(355,288)	(473,260)
1944	51.61	51.44	51.52	51.23
	(825,232)	(651,428)	(366,015)	(483,590)
1945	51.57	51.57	51.26	51.29
	(789,167)	(629,966)	(357,947)	(477,254)
1946	51.75	51.52	51.34	51.26
	(1,091,000)	(784,236)	(394,706)	(490,514)
1947	51.59	51.36	51.27	51.29
	(1,340,504)	(859,545)	(427,427)	(492,340)
1948	51.56	51.48	51.11	51.15
	(1,131,375)	(877,977)	(441,005)	(488,400)
1949	51.60	51.43	51.29	56.23
	(1,049,618)	(930,430)	(480,394)	(523,287)
1942–49	51.62	51.47	51.31	51.22
	(8,186,580)	(6,042,043)	(3,127,562)	(3,860,645)

were the same in the two periods. This figure is 51.472, little less than the observed value of 51.481 for 1942–46, and significantly higher than the observed figure of 51.406 for 1937–41 (difference 0.066 ± 0.021, critical ratio 3.1). The difference in sex ratio between the two periods cannot therefore be accounted for by changes in the birth rank distribution of births unless there were coincident changes in the sex ratio within individual birth ranks.

Although no comparable pre-war figures are available, it is of interest to examine the secular changes in sex ratio within individual birth ranks during the years 1942–49. This is done in table 1. In general the sex ratios for the years 1947–49 are lower than the means for the period, irrespective of birth rank. This is further evidence that the high sex ratio for 1942–46 is not the result of changes in birth rank distribution, and also suggests that the rise in sex ratio is not confined to any single birth rank. It is interesting to note however that within the period of high sex ratios (1942–46) individual birth ranks show different patterns. Thus, the high ratios noted in all white livebirths in 1942 and in 1946 are largely the result of high ratios in first births in these years. This is particularly so in 1946, where the sex ratio was outstandingly higher than the mean only in first births. The sex ratio of second births was highest in 1945 and that of third births in 1944.

AGE OF FATHER

Some early writers and more recently Novitski (1953) have suggested that sex ratio may be associated with age of father. Novitski, using United States

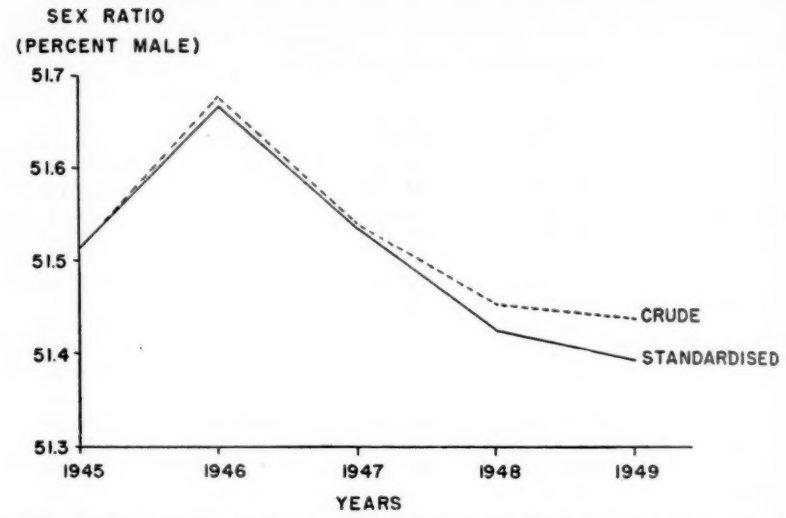

FIG. 3. Sex ratio of white livebirths, five selected states, 1945–49, with standardization for age of father. Standardized against the 1945 distribution by father's age.

Vital Statistics, concluded that sex ratio was more directly correlated with age of father than with age of mother. However, as already noted, age of mother seems not to be important when its correlation with birth order is taken into account. No data are yet available to examine the association with age of father independently of birth order or vice versa.

In attempting to examine the possibility that changes in distribution of births by age of father contributed to the observed secular changes in sex ratio, we are again limited by availability of data. Distribution by paternal age is not available separately for white births prior to 1945, and inclusion of non-white births might seriously bias the examination in view of the lower sex ratio of such births. However, for 1945–49, data on white births are available by age of father and sex and for each state, which makes possible a simple standardization procedure. The distribution of births by paternal age in 1945 in the five well-reported states is used as the standard population, and the sex ratios in each paternal age group in each subsequent year in these states are applied to this standard population. The results are shown in figure 3 and compared with the unstandardized figures shown previously. Certainly in these years and in these states changes in distribution of births by father's age did not contribute materially to the observed changes in sex ratio even though there were appreciable changes in distribution by father's age during this time.

DISCUSSION

These data support the belief that some factor or factors associated with war, or the end of war, influences the secondary sex ratio in man. A belief in the wisdom of Divine Providence in increasing the proportion of males born at such times is not essential to the rationalization of this relationship, although it must be admitted that no more satisfactory explanation is yet available. There is little doubt that the patterns of reproductive practices are disturbed during wartime. That these patterns were particularly disturbed in 1946 (the year of highest sex ratio) is suggested by the fact that the marriage rate of that year (16.4 per thousand) was the highest ever recorded in the United States. At the same time it seems unlikely that the high sex ratio of that year was the result of a high ratio in births resulting from marriages during that year, unless interval between marriage and birth of first child was extraordinarily short. There are no direct data on this question, but the percentage of first births was highest in 1947 which suggests that births in this year felt the greatest effect of the 1946 marriage peak. This is of interest in view of the observation that sex ratio of first births was particularly high in 1946 but not in 1947. Evidently births resulting from marriages occurring before the peak of the post war rush showed the greatest change in sex ratio.

The particularly striking peak of sex ratio in first births in 1946 suggests a more circumscribed population group which seems especially susceptible to this change in sex ratio and in which the explanation of the relationship between war and sex ratio might best be sought.

SUMMARY

Published vital statistics for the United States are used to examine the sex ratio of white livebirths during the years 1915 to 1949 with particular reference to the period of the Second World War. Justification is given for confining the examination to whites and livebirths.

For the Birth Registration Area as a whole there was a small, but statistically significant, increase in sex ratio in the period 1942 through 1946, with the peak attained in 1946. Examination of data from 5 states, (Connecticut, Massachusetts, New Jersey, New York, Rhode Island), in which, both in 1930 and in 1940, 98% or more of white livebirths were reported revealed a more marked increase in sex ratio affecting the years 1945–47, the peak occurring in 1946 being striking. The high sex ratio in 1946 was particularly noticeable in first births.

Evidence is presented which suggests that these secular changes in sex ratio were not the result of changes in distribution of births by age of mother, birth order, or age of father.

REFERENCES

BAUMGARTNER, L., WALLACE, H. M., LANDSBERG, E. AND PESSIN, V.: The inadequacy of routine reporting of fetal deaths. *Am. J. Pub. Health*, 39: 1549, (1949)

CIOCCO, A.: Variation in the sex ratio at birth in the United States. *Human Biol.* 10: 36 (1938).

LOWE, C. R. AND MCKEOWN, T.: The sex ratio of human births related to maternal age. *Brit. J. Social M.* 4: 75 (1950).

———— A note on secular changes in the human sex ratio at birth. *Brit. J. Social M.* 5: 91 (1951).

MCMAHAN, C. A.: An empirical test of three hypotheses concerning the human sex ratio at birth in the United States, 1915–1948. *Milbank Memorial Fund Quarterly* 29: 273 (1951).

MACMAHON, B. AND PUGH, T. F.: Influence of birth order and maternal age on the human sex ratio at birth. *Brit. J. Prev. Social M.* 7: 83 (1953).

MARTIN, W. J.: Sex ratio during war. *Lancet* 2: 807 (1943).

METROPOLITAN LIFE INSURANCE COMPANY. Statistical Bulletin 20: No. 4, 1. (1939).

———— 30: No. 6, 5 (1949).

NOVITSKI, E.: The dependence of the secondary sex ratio in humans on the age of the father. *Science*, 117: 531.

BOOK REVIEW

Psychotic and Neurotic Illnesses in Twins

By ELIOT SLATER, with the assistance of JAMES SHIELDS (Genetics Unit, Institute of Psychiatry, University of London). Medical Research Council, Special Report Series, No. 278. London, England: Her Majesty's Stationery Office, 1953. Pp. vi + 386. $4.75.

THIS RECENT REPORT from England is an interesting addition to an already imposing array of twin data in the literature relating to psychiatric disorders. Investigation was made of 295 cases (293 twin pairs, 2 sets of triplets) unselected except as they were encountered in a survey of hospital patients, and with a prerequisite that the twin partners had attained adult life. The author, or a psychiatric social worker, personally examined 271 of the propositi and 202 of the twin partners. Of the propositi, 156 had a clinical diagnosis of schizophrenia, and the remainder were divided about equally between affective psychosis, organic disorders, and psychopathic and neurotic states.

The twin pairs consisted of 67 uniovular and 224 binovular pairs, with 6 pairs listed as doubtful. Ovularity was determined by history and/or anthropomorphic data and fingerprint analysis; blood testing was little used. It was surprising to find in the tabulation of case histories that 16 of 37 cases listed under the heading of schizophrenic "uniovular pairs" were individually described as "? uniovular." Although this was probably an attempt of the author to be completely objective in describing his data, it caused this reviewer some concern. Thus, while expressing some question as to the ovularity of various twin pairs in his presentation of individual cases, the author in his extensive calculations has dropped the "?" and "probably" labels. Moreover, in his calculation of the percentage of uniovular twinning in his data (24%), the author arbitrarily solves the problem posed by 4 male same-sexed pairs of doubtful ovularity by relegating 2 of them to the uniovular group and 2 to the binovular group. This handling of the ovularity question appears to be a weak spot in the study, and unfortunately a crucial one. It is a point upon whose relative importance different readers will disagree, depending upon their individual demands for proof of ovularity. The author generalizes that in comparing twins side by side, "... it is nearly always easy to come to a final conclusion about the diagnosis of ovularity at once, as one can compare a great number of additional characteristics, such as small details of formations of the ear, the size and shape of the hands, fingers and fingernails, qualities of the skin, etc." (p. 27), but later refers to one pair "... though so similar physically as to be mistaken for a uniovular pair until blood grouping proved the contrary." (p. 45). It would appear to be a question of how much error to allow. The reviewer considers that any errors of classification that may be present probably don't affect the results appreciably, though he, like the author, is in no position to prove his point. The case histories of all pairs of "uniovular" and "doubtful ovularity" twins are carefully given in detail, so that each reader can judge for himself on the merits of the individual case.

This study agrees with other reports in emphasizing the role of heredity in the etiology of psychoses. For example, using corrective factors from his own data, the author found a concordance figure of 76% for schizophrenia in uniovular twins and 14% in binovular twins. The rather low incidence value of 5% for siblings was attributed to the less thorough examination of these individuals.

The monograph includes an excellent review of the literature. A long but systematic summary (52 short, numbered, paragraphs) gives a general picture of the scope of the study as well as a clear statement regarding the author's interpretation of his data. The 272 pages of case histories should be of considerable interest to the psychiatrist. The author has perhaps attempted to cover too much ground in his study, and could profitably have omitted such groups as epilepsy, whose 14 cases contribute little of significance. The inclusion of such information as that on breast feeding, which must obviously be of very questionable accuracy, and evaluations of intelligence which are not adequately documented, reflect on the remainder of the psychiatric data, which the reviewer is not in a position to properly evaluate. The monograph exemplifies well the difficulties of twin research and the evaluation of psychiatric disease. The author expresses it neatly when he says, "As in all such investigations it is with a sieve rather than a scoop that the human material is gathered." (p. 24).

This monograph is "must" reading for all those having an interest either in twin studies or in the genetic aspect of psychiatric disease. It would also make good required reading for all environmentally-directed psychiatrists. The report contains a wealth of data relating to the subject of twinning, dermatoglyphics, and especially to the clinical features of psychiatric disease, but it is impossible in this short review to deal with the many individual relationships investigated. The monograph is a valuable contribution by a very competent investigator toward the better understanding of a difficult subject.

RAY C. ANDERSON
University of Minnesota

BIBLIOGRAPHY OF HUMAN GENETICS

Prepared by
DR. V. RAE PHELPS
P. O. Box 614, East Lansing, Michigan

THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above any recent reference which has been missed or any current reference which it seems probably may be missed as a result of its appearance in a journal not systematically covered by the bibliographic editor. If a reference to an article or book is sent in be sure that it is complete with regard to author(s), title, year of publication, name of journal with volume number and first and last page numbers, or publisher and place of publication (if book).

AGNISETTA, S., & MASSENTI, S. 1953. Studi ematochimici sul disordine ematologico mediterraneo: emoglobina alcali-ristente. [Hematochemical studies in Mediterranean anemia alkali resistant hemoglobin.] *Minerva med.*, Tor. 44(75): 661–664.

ALLAN, T. M. 1953. ABO blood groups and human fertility. *Brit. J. Prev. Social M.* 7(4): 220–226.

ANDREANI, G., & CASTELLETTI, V. 1953. Sull'oligofrenia fenilpiruvica presentazione di un caso. [Phenylpyruvic oligophrenia; report of a case.] *Riv. neur.*, Tor. 23(2): 189.

ANDRÉ-BALISAUX, G. 1953. Incidence familiale et facteurs préparants dans l'encéphalite de la vaccination jennérienne; aspects électroencéphalographiques. [Familial incidence and predisposing factors in encephalitis due to jennerian vaccine; electroencephalographic aspects.] *Acta neur. psychiat. belg.* 53(7): 438–471.

BALTZER, Y. 1953. Pelger oder Pelgeroid? [Pelger or Pelgeroid?] *Schweiz. med. Wschr.* 83(43): 1031–1032.

BASS, M. H. 1952. Diseases of the pregnant woman affecting the offspring. *Adv. Int. Med.* 5: 15–58.

BAYS, R. P., & SCRIMSHAW, N. S. 1953. Facts and fallacies regarding the blood pressure of different regional and racial groups. *Circulation*, N. Y. 8(5): 655–663.

BEAVEN, G. H., & WHITE, J. C. 1953. Detection of foetal and sickle-cell haemoglobin in human anaemias. *Nature*, Lond. 172(4387): 1006.

BECKER, P. E. 1953. *Dystrophia musculorum progressiva. Eine genetische und klinische Untersuchung der Muskeldystrophien.* [Progressive muscular dystrophy. A genetic and clinical investigation of muscular dystrophy.] Stuttgart: Verlag.

BENNETT, J. H. 1954. On the theory of random mating. *Ann. Eugen.* 18(4): 311–317.

BENNETT, J. H., & BRANDT, J. 1954. Some more exact tests of significance for O-A maternal-foetal incompatibility. *Ann. Eugen.* 18(4): 302–310.

BLACK, R. L., LOWNEY, J. F., & DUFFY, P. M. 1954. Alcaptonuria and ochronosis; report of five cases occurring in an American family. *A. M. A. Arch. Int. M.* 93(1): 75–86.

BLACKETER-SIMMONDS, D. A. 1953. An investigation into the supposed differences existing between mongols and other mentally defective subjects with regards to certain psychological traits. *J. Ment. Sc.*, Lond. 99(417): 702–719.

BLOND, K. 1953. Cancer and heredity. *J. Internat. Coll. Surgeons* 20(5): 544–550.

BOGAERT, L. VAN. 1953. Sur une idiotie amaurotique de type infantile precoce, sans lesions carateristiques du fond d'oeil, dans une souche israelite. [Amaurotic idiocy of infantile precocious type, without characteristic lesions of the eyeball, in an Israelite family.] *Fol. psychiat. & neurl.* 56(4): 419–424.

BORNSTEIN, B. 1953. Familial early infantile myasthenia gravis. *Acta paediat.*, Upps. 42(5): 442–452.

BRIETINGER, E. 1952. Zur Methodik der Zwillingsdiagnose. [The method of twin diagnosis.] *Homo* 3(1): 5–21.

CALCHI-NOVATI, C., CEPPELLINI, R., BIANCHO, I., SILVESTRONI, E., & HARRIS, H. 1954. *B*-aminoisotutyric acid excretion in urine. A family study in an Italian population. *Ann. Eugen.* 18(4): 335–336.

CALLIGARIS, G. 1953. Due casi familiari di malattia periodica. [Two familial casts of periodic disease.] *Minerva pediat.*, Tor. 5(18): 781–784.

CANESTRINI, L., & PAPARO, F. 1953. Una melattia familiare di difficile classificazione. [Familial disease of difficult classification.] *Riv. neur.*, Tor. 23(3): 339–342.

CEPPELLINI, R., NASSO, S., & TECILAZICH, T. 1952. *La malattia emolitica del neonato.* [Hemolytic disease of newborn.] Milano: Instituto Sieroterapico Milanese Serafino Belfanti.

CHOWN, B., & LEWIS, M. 1953. The ABO, MNSs, P, Rh, Lutheran, Kell, Lewis, Duffy, and Kidd blood groups and the secretor status of the Blackfoot Indians of Alberta, Canada. *Am. J. Phys. Anthrop.* 11(3): 369–383.

CORSI, A. 1953. Un caso di paralisi parossistica. [A case of periodic paralysis.] *Folia hered. path.* 3(1): 8–17.

CUGUDDA, E., & AGNISETTA, S. 1953. Studi ematochimici sulle sindromi ematologiche mediterranee; la sideremia nelle forme minori delle sindromi ematologiche mediterranee. [Hematochemical studies on Mediterranean hematological syndromes; sideremia in minor forms of Mediterranean hematological syndromes.] *Minerva med.*, Tor. 44(70): 499–505.

DAHR, P. 1953. Möglichkeiten und Grenzen der Anwending der Erkenntnis der Blutgruppenforschung in der Gynäkologie. [Possibilities and limitations of application of the blood group research in gynecology.] *Deut. med. Wschr.* 78(44): 1509–1514.

DOMENCI, F. 1952. Gruppi, sottogruppi e fattori ematici: loro importanza nella pratica trasfusionale. [Blood, subgroups, and factors; their importance in blood transfusions.] *Clin. nuova*, Roma 15(21–23): 439–440.

DOBZHANSKY, T. 1953. A comment on the discussion of genetics by His Holiness, Pius Xii. Science 118(3071): 561–562.

DRIESSEN, O. A. 1953. De l'identité de la maladie de Tay-Sachs et de Niemann-Pick. [The identity of the Tay-Sachs and Niemann-Pick diseases.] *Acta paediat.*, Upps. 46(5): 447–452.

DUNSFORD, I. 1953. Family antigens or private blood groups and the sub-group of A-A_4. *Nature*, Lond. 172(4388): 1059.

FILITTI-WURMSER, S., JACQUOT-ARMAND, Y., AUBEL-LESURE, G., & WURMSER, R. 1954. Physico-chemical study of human isohaemagglutinins. *Ann. Eugen.* 18(3): 183–202.

FOWLER, E. P. 1954. Otosclerosis in identical twins: factors in onset, exacerbation, and stabilization. *J. Am. M. Ass.* 154(4): 304–306.

FRACCARO, M. 1953. Fenilchetonuria (oligofrenia fenilpiruvica) in una famiglia lombarda. [Phenylketonuria (oligophrenia phenylpyruvica): a family in Lombardia.] *Folia hered. path.* 3(1): 18–26.

FRACCARO, M. 1953. Zigodattilia recessiva con manifestazione differente in due fratelli.

[Recessive zygodactyly with different manifestations in two sibs.] *Folia hered. path.* 3(1): 113–114.

FRANCESCHETTI, A. 1953. Cas observe: rétinite pigmentaire récessive dans deux générations consecutives pseudo-dominance. [Case study: recessive retinitis pigmentosum in two consecutive generations (pseudo-dominance).] *J. génét. humaine*, Genève 2(2): 145-146.

FRASER, F. C. 1954. Medical genetics in pediatrics. *J. Pediat.* 44(1): 85–103.

FRASER, F. C., & SCRIVER, J. B. 1954. A hereditary factor in chondrodystrophia calcificans congenita. *New England J. M.* 250: 272–277.

FRICK, P. G., ; MC QUARRIE, I. 1954. Congenital afibrinogenemia. *Pediatrics* 13(1): 41–43.

GATTO, I., & VALENTINO, L. 1953. Thalassemia (microcarterocitosis) minima. *Pediatria*, Nap. 61(5–6): 313–335.

GIANFERRARI, A., CRESSERI, A., & MALTARELLO, A. 1954. Ricerche sulla ereditarieta dell'idroftalmo e della cataratta congenita in paesi delle Prealpi Orobiche. [Research concerning hereditary hydrophthalmos and congenital cataract in people of Prealpi Orobiche.] *Acta genet. med. gemellol.*, Roma 3(1): 1–15.

GOIRAND, R., & MARTIN-LAVAL, J. 1953. Isoimmunisation maternelle et maladie hémolytique du nouveau-né. [Maternal iso-immunization and hemolytic disease of the newborn.] *France med.* 16(8): 12–21.

GOMEZ DEL CAMPO, D., & STRAFFON OSORNO, A. E. 1953. Sindrome de Cooley minor en un nino mexicano. [Minor Cooley syndrome in a Mexican child.] *Bol. san. mil.*, Mex. 6(6): 163–178.

GOODALL, H. B., HENDRY, D. W. W., LAWLER, S. D., & STEPHEN, S. A. 1954. Data on linkage in man: elliptocytosis and blood groups III. Family 4. *Ann. Eugen.* 18(4): 325–327.

GOSSE, W. 1951. Untersuchungen über den serologischen Nachweis der heterozygoten Blutgruppen AO und BO. [Studies on the serological demonstration of the heterozygous blood groups AO and BO.] *Deut. Zschr. gerichtl. Med.* 40(7–8): 585–592.

GREBE, H. 1953. Contribution au diagnostic différentiel du syndrome de Bardet-Biedl. [Differential diagnosis of Bardet-Biedl syndrome.] *J. genet. humaine*, Genève 2(2): 127–144.

GREBE, H. 1954. Familienbefunde bei letalen Anomalien der Körperform. [Family findings in lethal anomalies of body form.] *Acta genet. med. gemellol.*, Roma 3(1): 93–111.

GREBE, H. 1954. Kindliche Entwicklungsstorungen durch praenatale Erkrankungen. [The developmental disturbances in infancy due to prenatal diseases.] *Folia hered. path.* 3(1): 27–53; (2): 126–154.

HAUGE, M., & HELWIG-LARSON, H. F. 1954. Studies on linkage in man. Red hair versus blood groups, P. T. C., and eye colour. *Ann. Eugen.* 18(3): 175–182.

HERNDON, C. N. 1954. Heredity counseling. *Eugen. Quart.* 1(1): 64–66.

HERNDON, C. N. 1954. Intelligence in family groups in the Blue Ridge Mountains. *Eugen. Quart.* 1(1): 53–57.

HOLT, S. B. 1954. Genetics of dermal ridges: bilateral asymmetry in finger ridge counts. *Ann. Eugen.* 18(3): 211–231.

HUSER, H. J. 1953. Beitrag zur Bedeutung des Morbus haemolyticus neonatorum in der Entwicklung isolierter Bevölkerungen. [Significance of morbus haemolyticus neonatorum in development of isolated populations.] *Schweiz. med. Wschr.* 83(43): 1045–1046.

IMPERATO, C. 1953. Sulla epidermolisi bollosa recessiva distrofica. *Pediatria*, Nap. 61(5–6) 389–424.

JACQUOT-ARMAND, Y., & FILITTI-WURMSER, S. 1953. Sur la concentration des isoagglutinines

anti-B dans les serums d'individus de genotype A_1O, A_1A_1 et OO. [Concentration of anti-B isoagglutinins in sera of individuals of genotype A_1O, A_1A_1, and OO.] *Arch. sc. physiol.*, Par 7(3): 233–239.

JANKIEWICZ, H. A., & ZANKAN, L. 1953. A three generation pedigree of the blue sclerotics syndrome. *Am. J. Optometr.* 30(11): 581–587.

KARN, M. N. 1954. Data of twins born in Italy (1936–1951). *Acta genet. med. gamellol.*, Roma 3(1): 42–49.

KLOEPPEL, W. 1953. Deckbiss bei Zwillingen. [Close-bite occlusion in twins.] *Fortsch. Kieferorthop.* 14(2): 130–135.

LARSON, C. A. 1953. Garber's toe deformity. *Acta genet.* 4: 414–416.

LAWLER, S. D., & SANDLER, M. 1954. Data on linkage in man: elliptocytosis and blood groups. IV. Families 5, 6, & 7. *Ann. Eugen.* 18(4): 328–334.

LENNOX, W. G. 1953. La herencia de la epilepsia; estudiada en los familiares de los pacientes y en gemelos. [Heredity of epilepsy, studies in families of patients and in twins.] *Pediat. Americas*, Mex. 10(6): 251–252.

LEWIS, D. 1953. A relationship between dominance, phenotypic stability and variability, and a theory of alternative genetic pathways. *Nature*, Lond. 172(4390): 1136–1137.

LICHTMAN, H. C., WATSON, R. J., FELDMAN, F., GINSBERG, V., & ROBINSON, J. 1953. Studies on thalassemia. I. An extracorpuscular defect in thalassemia major. II. The effects of splenectomy in thalassemia major with an associated acquired hemolytic anemia. *J. Clin. Invest.* 32(12): 1229–1235.

LINQUETTE, M., & RABACHE, R. 1953. Etude d'une famille atteinte de myotonie atrophique; remarques cliniques. [Study of a family afflicted with myotonia atrophica; clinical remarks.] *Echo mèd. nord.* 24(7): 246–247.

LOWE, C. R., & MCKEOWN, T. 1954. An investigation of dextrocardia with and without transposition of abdominal viscera, with a report of a case in one monovular twin. *Ann. Eugen.* 18(4): 267–277.

MCARTHUR, N. 1954. Changes in twin frequencies. *Acta genet. med. gemellol.*, Roma 3(1): 16–28.

MCARTHUR, N. 1954. The relative aetiological effects of maternal age and parity in biovular twinning. *Ann. Eugen.* 18(3): 203–210.

MCCARTY, R. T. 1953. The genetic factor of familial disseminated polyposis coli. *Am. J. Surg.* 86(5): 500–504.

MACKLIN, M. T. 1953. Inheritance of cancer in man. *Eugen. News* 38(4): 112–119.

MACMAHON, B., & GORDON, J. E. 1953. Epidemiologic inferences derived from maternal age. *Am. J. M. Sci.* 226(3): 326–349.

MACMAHON, B., PUGH, T. F., & INGALLS, T. H. 1953. Anencephalus, spina bifida, and hydrocephalus related to sex, race, and season of birth, and incidence in siblings. *Brit. J. Prev. Social. M.* 7(4): 211–219.

MALAGUTI, A. 1953. Sclere azzurre e fragilita ossea (osteopsatirosi) idiopatica (sindrome di Lobstein). [Blue sclera and idiopathic fragilitas ossium (osteopsathyrosis), Lobstein disease.] *Rass. clin. ter.* 52(3): 142–174.

MALTARELLO, A. 1953. El problema genetico della tuberculosi. [The genetic problem of tuberculosis.] *Minerva med.*, Tor. 44(81): 919–927.

MATSUNAGA, E. 1953. Intra-uterine selection by the ABO incompatibility of mother and foetus. *Proc. Japan Acad.* 29(7): 399–403.

MATSUNAGA, E., & ITOH, S. 1953. Intra-uterine selection by the ABO incompatibility of mother and foetus. II. *Proc. Japan Acad.* 29(9): 529–531.

METRAKOS, J. D. 1953. Congenital hypertrophic pyloric stenosis in twins. *Arch. Dis. Childh.*, Lond. 28(14): 351–358.

MOHR, J. 1954. Note on the inheritance of the Duffy blood group system and its possible interaction with the Rhesus groups. *Ann. Eugen.* 18(4): 318–324.

MOOR-JANKOWSKI, J. K. 1953. Die Blutgruppen- und Rh-Faktor-Verhältnisse in den westlichen Walsersiedlungen Graubündens. [Blood groups and Rh factor relations in western Walser settlements of Graubunden in Switzerland.] *Schweiz. med. Wschr.* 83(43): 1044–1045.

MORETTI, I. 1954. Comportamento della menopausa in gemelle mono- e biovulari. The menopause in mono- and biovular twins.] *Folia hered. path.* 3(2): 155–161.

MORETTI, I., & BALDI, M. F. 1953. La posizione del mongolismo fra le embriopatie. [The position of mongolism with regard to embryopathy.] *Folia hered. path.* 3(1): 81–112.

MOURANT, A. E. 1954. Blood grouping. *Brit. M. J.* No. 4852: 37–39.

MULLER, R. 1953. Genetic aspects of multiple sclerosis. *A. M. A. Arch. Neur. Psychiat.* 70(6): 733–740.

MUNDY-CASTLE, A. C., MCKIEVER, B. L., & PRINSLOO, T. 1953. A comparative study of the electroencephalograms of normal Africans and Europeans of Southern Africa. *Electroencephalography*, Montreal 5(4): 533–543.

MUTRUX, S., MARTIN, F., CHESNI, Y. 1953. Ataxie congénitale et familiale associée a des malformations somatiques, a des troubles oculaires et a des troubles mentaux. [Congenital and familial ataxia associated with skeletal malformations, ocular disorders and mental disorders.] *J. génét. humaine*, Genéve. 2(2): 103–116.

NIEDDU, G., & VENTURA, B. 1953. Aspetti odontostomatologici del morbo di Cooley. [Odontostomatological aspects of Cooley's disease.] *Minerva stomat.*, Tor. 2(4): 182–188.

OUNSTED, C. 1953. The sex ratio in convulsive disorders with a note on single-sex sibships. *J. Neur.*, Lond. 16(4): 267–274.

PENDER, C. B., & FRASER, F. C. 1953. Dominant inheritance of diabetes insipidus. *Pediatrics* 11(3): 246–254.

PENROSE, L. S. 1953. Hereditary influences in relation to the problem of child adoption. *Bull. World. Health. Org.* 9(3): 417–422.

PENROSE, L. S. 1954. Distance, size, and shape. *Ann. Eugen*, 18(4): 337–343.

PEREIRA, J. G., PONTES, J. T., PONTES, J. F., MANZIONE, A., SIMONSEN, O., & SILVA, R. R. DA. 1953. Adenomatose familiar múltipla do intestino grosso. [Familial adenoma of the large intestine.] *Rev. paul. med.* 43(1): 27–48.

PICKFORD, R. W. 1953. Inheritance of minor colour vision variations. *Nature* 171: 1167.

PINTUS, G., & SARTESCHI, P. 1954. Studio di un parentado affecto da una particulare malattia nervosa ereditaria. [Study of a family affected with a particular hereditary nervous disease.] *Folia hered. path.* 3(2): 162–173.

POLHEMUS, D. W., & SCHAFER, W. B. 1952. Congenital absence of the spleen; syndrome with atrioventricularis and situs inversus. *Pediatrics* 9(6): 696–708.

RAMON GUERRA, A. U., ESCANDE, C. A., MATEO, A. L., & VOLPE, A. 1953. Panhematopenia esplenica familiar. [Familial splenic panhematopenia.] *Arch. pediat. Uruguay* 26(7): 433–443.

RANNEY, H. M., LARSON, D. L., & MCCORMACK, G. H., JR. 1953. Some clinical, biochemical and genetic observations on hemoglobin C. *J. Clin. Invest.* 32(12): 1277–1284.

REVAULT, P. P., TRAEGER, J., & TOURAINE, R. 1953. Formes familiales de la spondylarthrite ankylosante. [Familial forms of ankylosing spondyloarthritis.] *Rev. rhumat.*, Par. 20(6–7): 516–517.

REED, S. C., REED, E. W., & PALM, J. D. 1954. Fertility and intelligence among families of the mentally deficient. Eugenics Quart. 1(1): 44–52.

REICH, R. S., & ROSENBERG, N. J. 1953. Aseptic necrosis of bone in Caucasians with chronic hemolytic anaemia due to combined sickling and thalassemia traits. *J. Bone Surg.* Am. Vol. 35-A(4): 894–904.

REYNAIERS, H. 1953. Cutis laxa hyperelastica (syndrome d'Ehlers-Danlos). *Arch. belg. derm. syph.* 9(1): 29–30.

RIFE, D. C. 1953. An investigation of genetic variability among Sudanese. *Am. J. Phys. Anthrop.* 2(2): 189–202.

ROSENFIELD, R. E., VOGEL, P., GIBBEL, N., OHNO, G., & HABER, G. 1953. Anti-Jk^a: three new examples of the isoantibody; frequency of the factor in Caucasians, Negroes, and Chinese of New York City. *Am. J. Clin. Path.* 23(12): 1222–1225.

SACHS, L. 1954. Sex-linkage and the sex chromosomes in man. *Ann. Eugen.* 18(3): 255–261.

SANGER, R., RACE, R. R., ROSENFIELD, R. E., & VOGEL, P. 1953. A serum containing anti-s and anti-Jk^b. *Vox Sanguinis* 4: 71.

SANGER, R., RACE, R. R., ROSENFIELD, R. E., VOGEL, P., & GIBBEL, N. 1953. Anti-f and the "new" Rh antigen it defines. *Proc. Nat. Acad. Sci.* 39(8): 824–834.

SANGHVI, L. D. 1953. Comparison of genetical and morphological methods for a study of biological differences. *Am. J. Phys. Anthrop.* 11(3): 385–404.

SCHOLTEN, C. 1953. Konstitutionbiologische Gesichtspunkte zur Fettsucht im Kindesalter. [Constitutional-biological aspects of the obesity in childhood.] *Med. Klin.*, Berl. 48(46): 1696–1698.

SCOTT, J. P. 1953. New directions in the genetic study of personality and intelligence. *Eugen. News.* 38(4): 97–101.

SECRÉTAN, J. P. 1953. La surdi-mutité récessive est-elle d'origine peripherique ou centrale. [Peripheral or central origin of recessive deaf-mutism.] *J. gênêt. humaine*, Genéve 2(2): 117–126.

SHANDS, A. R., JR., & WENTZ, I. J. 1953. Congenital anomalies, accessory bones, and osteochondritis in the feet of 850 children. *Surg. Clin. N. America*, Philadelphia No. 1643–1666.

SHIELDS, J. 1954. Personality differences and neurotic traits in normal twin school children. *Eugen. Rev.* 45(4): 213–146.

SIEHL, D. 1953. Heredity in spondylolisthesis and spondylolysis. *J. Am. Osteopath. Ass.* 53(3): 154–156.

SIMMONS, R. T., GRAYDON, J. J., & SEMPLE, N. M. 1953. A further blood genetical survey in Micronesia: Palauans, Trukese and Kapingas. *Med. J. Australia* 40:2(16): 589–596.

SLUNGAARD, R. K., & HARRIS, L. E. 1953. Chrondrodysplasia (achondroplasia) in one of dizygotic twins. *A. M. A. Am. J. Dis. Child.* 86(6): 788–794.

SMITH, C. A. B. 1954. The separation of the sexes of parents in the detection of linkage in man. *Ann. Eugen.* 18(4): 278–301.

SMITH, M. 1953. Familial incidence of sialectasis. *Brit. M. J.* No. 4850: 1359.

SMITH, S. M. 1954. Discrimination between electro-encephalograph recordings of normal females and normal males. *Ann. Eugen.* 18(4): 344–350.

SPAET, T. H., ALWAY, R. H., & WARD, G. 1953. Homozygous type c hemoglobin. *Pediatrics* 12(5): 483–490.

SPEISER, P., & JANCIK, E. W. 1953. Über den immunbiologischen Antagonismus zwischen

den klassischen Blutgruppen und den Blutfaktoren beim Zustandekommen eines faktorenbedington Morbus haemoluticus neonatorum. [Immuno-biological antagonism between blood groups and blood factors in morbus hemolyticus neonatorum.] *Klin. Wschr.* 31(41–42): 995–997.

STECHER, R. M. 1954. Heberdeen's nodes: concordant osteoarthritis of the fingers in identical twins. *Acta gente. med. gemellol.*, Roma 3(1): 84–92.

STECHER, R. M. 1954. Heredity of joint diseases. *Eugenics Quart.* 1(1): 16–20.

STILES, K. A. 1954. Heredity and the optometrist. *Opt. J. & Rev. Optom.* 41(2): 35–39.

SUSSMAN, L. N. 1953. The Rh blood factor: genetic aspects of erythroblastosis. *Eugen. News* 38(4): 102–106.

TEPLITZ, R. L. 1953. Fibrocystic disease of the pancreas; general review and report of two cases occurring in identical twins. *J. Am. Osteopath. Ass.* 53(3): 156–158.

TILLNER, I. 1954. Über die Vierfingerfurche und ihre Übergangsformen, inbesondere bei Zwillingen. [Four-finger-crease and its transitional forms especially in twins.] *Acta genet. med. gemellol.*, Roma 3(1): 50–83.

TISSERAND-PERRIER, M. 1953. Etude comparative de certains processus de croissance chez les jumeaux. [Comparative study of certain growth processes in twins.] *J. Génét. humaine*, Genéve 2(2): 87–102.

TRAISMAN, H. S., & JOHNSON, F. R. 1954. Arachnodactyly associated with aneurysm of the aorta. *Am. J. Dis. Child.* 87(2): 156–166.

VANDEPITTE, J., CLAESSENS, H., & MARTEN, M. 1953. Tuberculose et sicklemie. Tuberculosis and sickle-cell trait. *Ann. Soc. belge med. trop.* 33(3): 259–267.

VENNING, P. 1954. Sib correlations with respect to the number of phalanges on the 5th toe. *Ann. Eugen.* 18(3): 232–254.

VOLTZ, H. 1953. Ein Beitrag zum Morbus Boeck-Besnier-Schaumann; zwei Erkrankungsfälle bei Geschwistern. [Morbus Boeck-Besnier-Schaumann; two cases in brother and sister.] *Deut. med. Wschr.* 78(46): 1598–1599.

VOTO BERNALES, J. COSTA, G., & ROMERO, J. 1952. Distrofia miotónica de Steinert: estudio familiar. [Steinert's myotonic dystrophy; study of familial aspects.] *An. Fac. med.*, Lima 35(4): 411–422.

WAIT, L. P. 1953. Congenital hypertrophic pyloric stenosis in identical twins. *Med. J. Australia* 40:2(18): 678.

WEDGEWOOD, R. J. P., COOK, C. D., & COHEN, J. 1953. Dermatomyositis. Report of 26 cases in children with a discussion of endocrine therapy. *Pediatrics* 12(4): 447–466.

WIENER, A. S., GORDON, E. B., & COHEN, L. 1954. Studies on the heredity of the human blood groups. II. The A-B-O groups. *Acta genet. med. gemellol.*, Roma 3(1): 29–33.

WIENER, A. S., NAPPI, R., & GORDON, E. B. 1953. Studies in Rh sensitization. VI. A-B-O blood groups and Rh subtypes in sensitized and nonsensitized Rh negative pregnant women. *Blood*, Balt. 8(11): 1024–1028.

WIENER, A. S., UNGER, L. J., & GORDON, E. B. 1953. Fatal hemolytic transfusion reaction caused by sensitization to a new blood factor U: report of a case. *J. Am. M. Ass.* 153(16): 1444-1446.

WILDERVANCK, L. S. 1954. A deaf-mute and a "hearing-mute" uniovular twin. *Acta genet. med. gemellol.*, Roma 3(1): 34–41.

WILLIAMS, R. J., & ROGER, L. L. 1953. The formulation of a genetotrophic supplement for the experimental treatment of diseases of obscure etiology. *Texas Rep. Biol. M.* 1(3): 573–581.

YOUNG, L. E., & MILLER, G. 1953. Differentiation between congenital and acquired forms

of hemolytic anemia; observations on 47 cases of hereditary spherocytosis and 24 cases of autoimmune hemolytic disease. *Am. J. M. Sc.* 226(6): 664–673.

ZIRKLE, C. 1954. Father-Adam and the races of man: some notes on medieval anthropology. J. Hered. 45(1): 29–34.

ZOUTENDYK, A., KOPEC, A. C., & MOURANT, A. E. 1953. The blood groups of the Bushmen. *Am. J. Phys. Anthrop.* 11(3): 361–368.

cases

ology.

men.